JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

VOL. XXVI APRIL, 1937 No. 4

W. G. CROCKETT.*

PRESIDENT, AMERICAN ASSOCIATION OF COLLEGES OF PHARMACY.

William Goggin Crockett, as vice-president, has succeeded the late Theodore J. Bradley as president of the American Association of Colleges of Pharmacy. His early education was obtained at Hampden—Sydney College; later, he studied at New York University where he earned his Master of Science Degree. The degree of Doctor of Pharmacy was awarded to him by Columbia University.

Prior to entering teaching Dr. Crockett had industrial experience as chemist with the Department of Health of New York City, with E. R. Squibb and Sons and with the du Pont Company. During the World War he served in the analytical research division of the Chemical Warfare Service, Washington, D. C.

In 1919, he became Professor of Pharmacy, Baylor University, Dallas, Texas, leaving there in 1920 to take the Chair of Pharmacy at the Medical College of Virginia, which he has since occupied. He has served as Chairman of the Section on Practical Pharmacy and Dispensing, AMERICAN PHARMACEUTICAL ASSOCIATION, as Chairman of the Conference of Teachers of Pharmacy, American Association of Colleges of Pharmacy. He is editor of the *Bulletin* and Chairman of the Virginia Section of the American Chemical Society. Dr. Crockett is a member of the General Committee of Revision of the United States Pharmacopœia and a member of the Board of Review of Papers of the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION.

* Data for this sketch have been taken from the *Richmond News Leader*, February 13, 1937, communicated by President W. T. Sanger, of the College.

EDITORIAL

E. G. EBERLE, EDITOR 2215 Constitution Ave., WASHINGTON, D. C.

COÖPERATION IN PUBLIC HEALTH WORK AND IN RESEARCH PROBLEMS.

THE campaign for stamping out syphilis is well under way because Surgeon General Parran has carried his message to the Public Health groups and also to the general public. He has not been afraid to bring his plan to the press as an undertaking for the control of a very dangerous disease and the subject has been discussed in the papers and magazines with an understanding that a public service is being rendered, for which a tremendous amount of popular education is needed to overcome the accompanying many great difficulties.

Dr. Parran has called upon and enlisted the coöperation of pharmacists and the effort so well begun must not stand still. He was elected president at the recent convention of the American Public Health Association in New Orleans and, prior to that meeting, a largely attended conference was held in Washington. The emphasis must be laid on "continuous effort," and only through that will the Surgeon General receive the support he has asked for and is entitled to for the public service he is rendering. The campaign has, no doubt, impressed the public with the importance of its part and that united and determined efforts have laid low other diseases that were a menace in their day. Some may say that this disease should not be discussed in connection with a disease that is not of its type.

The Surgeon General has said "All of us together—physician, public official and private citizen—must learn that this is everybody's business, that everybody is endangered, that everybody pays for it, whether afflicted by the disease or not, and that no single agency is big enough or clever enough to do every one's job alone."

Notwithstanding the organized efforts to control the spread of tuberculosis, the number suffering and dying because of the affliction, is large.

Cancer is a destructive scourge; it took more than 140,000 lives in the United States last year and, probably, three times that number are afflicted with it. The lives of many can be saved and to a certain extent the disease can be controlled by early recognition and coöperative effort to check its advance. Herein may be an opportunity for research, as stated at the meeting of the American Association for the Advancement of Science.

The importance of the affliction was given recognition in Congress by the introduction of a bill by Senator Bone of Washington and all Senators have sponsored the measure, which appropriates one million dollars yearly for research into the causes of cancer. The work will be carried on at the direction of Surgeon General Parran, who is authorized:

"(1) To make grants-in-aid to schools, clinics, hospitals, laboratories and other institutions, and to scientific investigators, whose work has shown promise of making valuable contributions to human knowledge with respect to the cause, diagnosis, control, treatment or prevention of the disease of cancer.

"(2) To purchase radium and lend such radium to institutions, state or privately controlled, for use in the treatment of such disease.

"(3) To establish in any marine hospital or other hospital under the supervision of the Public Health Service, or in any other hospital of the United States, with the consent of the chief executive officers of the executive department or agency under whose supervision such hospital is placed, a department for research and the clinical study of such disease, and

"(4) To pursue any other method which he may deem necessary to carry out the provisions of this act."

Turning aside to other research subjects that are not directly in line, the Government has reviewed means of insect destruction and soil study, which may offer suggestions to pharmacists and require the service of pharmacists in divisions of the Government. The U. S. Department of Agriculture in its *press service* advises that the wide-spread and increasing interest in soil conservation calls for a new specialist trained in all phases of erosion control technique. Similar conservation forces in colleges and universities, and adequate work in CCC camps aim to develop these specialists.

The messages of the comment are varied, but pharmacists have contributed to various arts, industries and developments.—See November JOURNAL, 1936, page 963.

"FIRST AID WEEK."

The days for "First Aid Week," have been fixed for May 16th to 22nd; the National Association of Retail Druggists has prepared a proclamation for signature by Mayors or City councils, and for publicity in the newspapers.

A *Bulletin* is published in the July issue of the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, for 1928, pages 699 to 701. This *Bulletin*, prepared under the direction of the Surgeon General, U. S. Public Health Service contains valuable information relating to the subject. It advises that every one become familiar with first-aid methods for treating the injured, and defines "first aid" as the temporary care of an injured person by simple, common sense methods, based on principles of medicine and surgery, that may be applied easily by persons not professionally trained in those subjects. It should be noted that the work of first aid ceases when the injured person has been turned over to the care of a physician. In the May JOURNAL of the same year, page 485, cases are cited which may be of value.

The Surgeon General states that, in addition to the benefits gained by the early care of the injured, first aid has been found actually to tend to lower accidents by making the people more careful.

"First Aid Week" presents an opportunity for pharmacists to make the public acquainted with "first aid" items and household medicines. The publicity may be brought to the attention of the public in the windows and by in-door displays and looked upon, if properly arranged, as a real service to the laity and professional pharmacy. Treatments of insect bites, plant and other poisons are closely related; formulas and means are given in the Pharmaceutical Recipe Book II.

THE PURPOSE AND METHOD OF THE ROCKEFELLER FOUNDATION.

A review for 1936 of the Rockefeller Foundation by Raymond B. Fosdick has been published. The purpose of the Foundation, written into its charter, is to promote the well-being of mankind throughout the world. "Changing conditions in scientific and social development must necessarily affect decisions as to how that purpose can best be realized. Nevertheless, for a decade or more, the advance of knowledge, with research the chief tool, has been the definite objective and method of Foundation action. The program has extended into the fields of natural science, social science, medical science, the humanities and public health. Except in public health the Foundation is not operating an organization. It conducts no researches of its own. Its efforts are limited to the support of other agencies—universities, laboratories, research institutes—where the promise of results seems particularly bright."

SCIENTIFIC SECTION

BOARD OF REVIEW OF PAPERS.—*Chairman*, F. E. Bibbins; H. M. Burlage, W. G. Crockett, E. V. Lynn, C. O. Lee, L. W. Rising, L. W. Rowe, Heber W. Youngken, F. V. Lofgren, J. C. Krantz, Jr.

OBSERVATIONS ON THE MENTHOL CONTENT OF OIL OF JAPANESE MINT UNDER CONTINUOUS CULTIVATION IN ONE LOCALITY.

BY A. F. SIEVERS AND M. S. LOWMAN.[1]

About 15 years ago the Division of Drug and Related Plants of the Bureau of Plant Industry became interested in the possibilities of the Japanese mint (*Mentha arvensis*, **var.** *piperascens* Malinvaud) as a commercial crop in the United States. The world supply of natural menthol, which is obtained exclusively from this species of mint grown in Japan, had been subject for some time to extreme fluctuations resulting some years in exceedingly high prices and uncertainty among the important consumers of this commodity as to an available supply from year to year. The fact that the cultural requirements of this mint are, on the whole, very similar to those of the American mint suggested that its introduction in some localities in the United States would not be difficult and that it might be at least as profitable as American mint if the higher prices of imported menthol that prevailed at that time were maintained. No detailed reports of experiments with this mint in the United States could be found. Therefore, this division undertook an investigation of this problem in 1922 which continued until 1931. Four main questions were considered: (1) The adaptiveness of this mint to various sections of the country and to various soil types; (2) the cultural practices required and the yields of oil that might be expected; (3) the menthol content of the oil, free and combined, and (4) the effects of continuous culture in any one locality on the menthol content and therefore on the usefulness of the oil for menthol production. The results of these investigations were published by the writers in 1933 as *Technical Bulletin* 378, U. S. Department of Agriculture, "Commercial Possibilities of Japanese Mint in the United States as a Source of Natural Menthol." With regard to questions 3 and 4 above, the summary in this bulletin states that "oil of satisfactory quality can be produced in this country" and that "continuous cultivation over a period of years indicates that seasonal conditions cause fluctuations in the menthol content of the oil but there is no general tendency for the menthol content to decline gradually as a result of the prevailing conditions in any one locality."

The foregoing conclusions are based on data from many sections but particular attention was called to the quality of the oil obtained year by year from a small bed of the mint on heavy clay loam soil at Arlington Farm, Rosslyn, Va. Data on the oil from six consecutive years were available from this bed in which the only cultivation during the period consisted of a light stirring of the soil in the spring and hand weeding during the season as necessary. The complete data are included in the table presented herewith which also includes data subsequently obtained.

[1] Bureau of Plant Industry, U. S. Department of Agriculture.

TABLE I.—THE YIELD, SOME PHYSICAL CONSTANTS AND MENTHOL CONTENT OF OIL FROM JAPANESE MINT OBTAINED UNDER CONTINUOUS CULTURE ON THE SAME GROUND FOR A PERIOD OF YEARS.

Year.	Date of Cutting.	Stage of Maturity.	Yield of Oil from Fresh Herb, Per Cent,	Physical Constituents of Oil. Color.	Specific Gravity 20° C.	Index Refraction 20° C.	Angle of Rotation.	Menthol in Oil. Combined, Per Cent.	Free, Per Cent.	Total, Per Cent.
1923	Aug. 20	Early blooming	0.39		0.8966	1.4560	−43.0	9.19	72.34	81.53
1924	Sept. 5	Full bloom	0.21		0.8973	1.4550	−43.5	9.75	68.10	77.85
1925	Sept. 17	Past blooming	0.30					7.24	76.37	83.61
1926	Sept. 20	Full bloom	0.29	Very pale straw	0.9001	1.4580		9.34	71.37	80.71
1927	Sept. 12	" "	0.22	Greenish yellow	0.9006	1.4590		11.03	71.25	82.28
1928	Sept. 14	" "	0.28	Slightly yellow	0.9001	1.4592		10.03	67.40	77.43
1929	Sept. 16	" "	0.35		0.8999	1.4560		8.23	70.68	78.91
1931	Sept. 17	" "	0.33		0.9001	1.4589		8.01	70.02	78.03
1932	Sept. 20	" "	0.30		0.8998	1.4588		7.78	72.02	79.80
1933	Sept. 11	" "	0.36					12.54	72.14	84.68
1935*	Sept. 9	" "	0.28*	Very pale straw	0.9040	1.4580		17.41	69.15	86.56
1936	Sept. 14	" "	0.48	Very pale straw	0.9017	1.4577		13.93	71.36	85.29

* Distilled Sept. 14, 1936. Yield calculated on basis of 75 per cent moisture in fresh herb.

In view of the fact that there were only seasonal fluctuations in the menthol content of the oil from this bed and no permanent decline in this respect could be discerned, the planting was continued after 1928, the last year for which data were reported in the bulletin.

There was no change in the cultural handling as described until the fall of 1932 when, due to the difficulty of further controlling weeds, the bed was spaded, the roots removed, manure added and the roots replanted in rows. This procedure resulted in a much improved growth in 1933 and a much larger total yield of oil. In the spring of 1934 a new bed near the old one and with the same type of soil was set with plants from the old bed. This was a year of extreme drought and insufficient growth was obtained to make a distillation. For a similar reason data are also lacking from the old bed in 1930. It is possible, therefore, to report at this time on the results obtained from the same original planting stock on the same soil type in a single locality for the period 1922 to 1936, except for the two years mentioned.

It will be noted from the tabulated data that from 1928 to 1932, inclusive, the total menthol content remained about the same, being slightly below 80 per cent. During the five years prior to 1928 a content below 80 per cent was obtained only in 1924. In 1933, after the bed had been spaded, fertilized and reset the total methol content was much higher and the same results have been obtained in the last two seasons.

The percentage of combined menthol increased in 1927 and 1928, then declined until 1933 and since then has been higher than in any previous year. The extent

to which the increase in the ratio of combined to free menthol is due to the replanting in the old bed or to the transfer of the stock to the new bed the following year is an open question. The fact that the herb cut in 1935 was not distilled until the fall of 1936, as indicated in the table, may be responsible in part for the unusually high percentage of combined menthol in the oil of that year.

From a practical standpoint a high percentage of free menthol rather than of total menthol is desired. When menthol is high in price, saponification of the oil may be resorted to in order to recover the menthol not present in the free state but under other conditions only the free menthol content determines the value of the oil as an economical source of that product.

Commercial mint fields are seldom maintained longer than four or five years even under the best conditions and the results reported in the bulletin showed quite conclusively that no serious decline in the quality of the oil is indicated during the normal life of a mint field. The question remained, however, whether the establishing of new fields with plants or roots from old fields in the same locality could be continued indefinitely without decline in the percentage yield or quality of the oil or even in the yield of the herb. If such a decline occurs and is due to continuous growing of the same stock in a specific locality it would be necessary for the grower to secure new planting stock from other regions. This would add to his production costs and introduce some uncertainty. The data obtained subsequent to 1928 appear to show, however, that such is not the case and that by planting new fields at such intervals as may be required under the prevailing conditions the securing of planting stock from other regions is not necessary. American peppermint oil has been produced in this country for many years and no general change in its quality has taken place where local planting stock is used for replacements indefinitely. It could not be reasoned from this, however, that the Japanese mint would behave similarly. The menthol content of its oil is much higher than that of the American mint oil and this characteristic might conceivably be modified by climatic and cultural conditions, not immediately perhaps, but possibly gradually. Moreover, it was the view of some that oils of high menthol content cannot be produced with consistency in this country, especially in the south, a view that was certainly not based on known facts when these investigations were begun. That it it is an erroneous view with respect to the region where these experiments were conducted has been clearly shown.

THE BARK OF AMERICAN LARCH.*

BY K. E. LARSEN AND E. V. LYNN.[1]

Together with other parts of the tree, the bark of American larch, *Larix americana* (Muench) Michx., has been employed as a remedy since earliest times. Several of the Indian tribes held it in high esteem as treatment for chronic bronchitis, inflammation of the urinary passages and in phases of hemorrhage. They considered it "equal to one man and a medicine in itself, without the addition of any

* Scientific Section, A. PH. A., Dallas meeting, 1936.

[1] Massachusetts College of Pharmacy, Boston, June 20, 1936.

other ingredient." The early white settlers adopted these traditions entirely and seem to have gradually added to the applications. Thus, in 1860 the bark was described as laxative, tonic, diuretic and alterative and was recommended in obstructions of the liver, in rheumatism, in jaundice and in cutaneous diseases. The main reputation, however, appears still to be in chronic bronchitis with profuse secretion, in which it is frequently combined with other drugs.

In spite of this use, sustained over several hundred years, no record could be found of any chemical examination of the bark. It is true that we might expect to find a composition similar to that which is known about the bark of other species of *Larix*, but so far no one has been interested enough to make a study.

The bark which was used in the present work was collected near Westminster, Massachusetts, in the late fall of 1934. It was first dried in the air, with a loss in weight of 27 per cent, and then ground to a number twenty powder. A partial analysis by the usual methods gave the following results, based on the air-dried bark.

Volatile at 110° C.	6.50
Ash	2.12
Acid-insoluble ash	0.22
Crude fiber	29.70
Starch, by acid hydrolysis	14.03
Pentosans	7.80
Tannins	6.49
Alcoholic extract	20.96
Diluted alcoholic extract	21.74
Successive extractions	
Benzin, volatile	0.22
non-volatile	4.19
Ether, volatile	0.60
non-volatile	5.50
Alcohol	14.65
Water	4.15

The tannins were found to be of the catechol type, since they gave a greenish brown precipitate with ferric salts and a light brown one with bromine water. They also gave the usual ones with gelatin, potassium chromate and dichromate and copper sulfate.

The aqueous extract gave a voluminous and persistent froth when shaken, indicative of saponins. The presence of these was still further confirmed by ability to form emulsions of oils and mercury and by precipitations. The characteristic laking of blood was not, however, obtained because the hemoglobin was precipitated by solutions of the bark, forming a dense, purple product.

About 10 per cent of the bark consisted of a brick-red resin which was obtained from the alcoholic extract by concentration and precipitation with water. It was quite hard and brittle and could easily be reduced to a fine, tasteless powder. Direct determination of the resin acids was impracticable because of the high color but 38 per cent of the resin dissolved in solutions of sodium and ammonium carbonate.

The aqueous solution, after precipitation of resins, was treated with normal and basic lead acetate to remove other substances and, after removal of the lead, concentrated to a small volume. Nothing separated until the solvent was nearly gone and the residue was evidently sugar. Certainly no crystalline glucoside was observed.

Tests for alkaloids were negative. Extraction was made both by acidified water and by alcohol, the latter solvent being removed by distillation under reduced pressure. In both cases the acid solution was treated with several of the alkaloidal reagents, but no precipitate was formed in any case.

The ash contained a notable quantity of manganese which was suspected because of the green color. The identification was confirmed by the usual qualitative procedure.

By distillation of the bark with steam, there was obtained a white, aromatic solid which was not acid and was soluble in ether. The odor was somewhat like borneol but no oxime or semicarbazone could be obtained from the oxidized product. The original substance melted under 60° C. but this was very indefinite. It was apparently a paraffin hydrocarbon mixed with some odorous substance. The amount obtained was too small to admit of a more careful examination.

SUMMARY.

A partial analysis was made of the bark of American larch and the results were tabulated. It contained starch, pentosans, tannins of the catechol type, saponins and 10 per cent of hard, brittle resin, partly acid, but no alkaloid. By steam distillation there was obtained a small amount of white solid which may be paraffin.

THE UNITED STATES PHARMACOPŒIAL STANDARD DIGITALIS POWDER.*

BY CHARLES W. EDMUNDS, CARL A. MOYER AND JAMES R. SHAW.

Ann Arbor, Michigan.

One of the points of difficulty which has been encountered in connection with the biological standardization of drugs has been the necessity of supplying some standard preparation of uniform potency against which the strength of the unknown might be measured and in terms of which its value could be expressed. While this is true for all the drugs which are subjected to this form of assay, it is of special importance in connection with the members of the digitalis series on account of their wide-spread use in circulatory disorders and the well-recognized variability of the crude drugs. At the same time digitalis itself offers special difficulties, as it contains no active principle which is suitable for use as a standard. Accordingly, in the U. S. P. IX, which was issued in 1916, and the first pharmacopœia in which biological standardization was recognized officially, crystalline *g*-strophanthin (ouabain) was adopted as the standard for members of the digitalis group of drugs. This glucoside was selected for the reason that pharmacologically it belongs to the digitalis series and chemically it is easily identified by its physical characteristics such as solubilities, melting point, etc. For the next twenty years, therefore, ouabain served as the standard in the United States for digitalis and its allies and, on the whole, it proved quite satisfactory. However, at the Edinburgh conference held in 1924 under the auspices of the Health Committee of the League of Nations, it was pointed out that, while ouabain was satisfactory as a standard for preparations of strophanthus, it was not suitable as a standard for digitalis for international usage. This was due to the different species of frogs which are in use in European countries and to the different methods of assay which are employed, factors which make it practically impossible to get comparable relationships between ouabain and digitalis in assays carried on in the different countries.

Accordingly, at this conference it was decided to investigate the possibility of

---

* From the Laboratory of Pharmacology of the University of Michigan. Supported in part by a grant from the Board of Trustees of the U. S. Pharmacopœia.

using a powder of digitalis as a standard for that drug, and Professor Magnus of Utrecht undertook its preparation, using the Hatcher-Brody cat method of assay as it had been modified at the University of Utrecht. The Edinburgh experimental powder, when injected in the form of an infusion, proved fatal to cats in a dose of 91.1 mg. per Kg. of body weight of cat. Since a cat unit had been defined as the amount of drug which will kill one kilo of cat, this powder contained 10.9 cat units in each gram of powder. As a result of this work, the Geneva conference held the next year, adopted as an International standard a powder of digitalis which should be prepared by Professor Magnus and be within ten per cent of the potency of the Edinburgh powder. Such a powder was secured by mixing ten different lots of powder obtained from various sources and when these were finally blended and assayed on twenty-three cats, the fatal dose was 89.7 mg. per Kg. of cat. Each gram therefore contained 11.1 cat units. This powder sealed in ampuls, containing about three Gm. each, serves to-day as an International standard. An International Digitalis unit is defined as being the equivalent in potency of 0.1 Gm. of the International standard powder and the U. S. P. Digitalis unit is identical in potency with the International unit. The International standard powder is stored in London and is furnished to the different countries to be used as a standard, and in turn each country prepares its own standard powder which is assayed and its potency determined in terms of the International Powder.

One of the first countries to adopt this standard and to prepare its own powder was Great Britain. The standard powder prepared for that country in 1928 and adopted by the British Pharmacopœia of 1932 was made by the careful drying and thorough mixing of nine different samples of dried leaves. It was assayed in terms of the International Powder both by the frog lethal dose method and by the cat method. In comparison with the International standard it possesses a potency of 138 per cent when assayed on frogs and judged by this method it contains 13.8 digitalis units per gram. On the other hand when assayed on cats it has a potency of 116 per cent, each Gm. therefore containing 11.6 digitalis units. According to these figures one International digitalis unit is contained in 0.0725 Gm. of the British powder when the assay is carried out by the frog lethal dose method and in 0.0862 Gm. when it is assayed on cats. When other methods of assay are used it is suggested that the intermediate figure of 0.079 Gm. be taken as representing one "unit."

The Canadian standard powder (No. 428) of 1928 also possesses a potency greater than the International in that 0.85 Gm. of the former is equivalent to 1 Gm. of the latter. The lethal dose (twelve to eighteen hours) method using frogs (*R. pipiens*) was employed in assaying this powder.

In the United States the new Pharmacopœia (XI), which became official on June 1, 1936, adopted a powder of digitalis as a standard for digitalis in place of ouabain, it being understood that its potency was to be determined in terms of the International standard. Such a powder was secured by blending three separate powders all of which had been carefully selected and dried. Two-thirds of the amount was from an American source, while one-sixth was secured from England and one-sixth from Germany. In the study of this composite specimen it was decided not only to determine its potency in terms of the International Powder but also in relation to the British and the Canadian standards. Such a study would not only serve as a check upon the accuracy of the methods employed but in addition might furnish valuable information upon the relative strengths of the different standards.

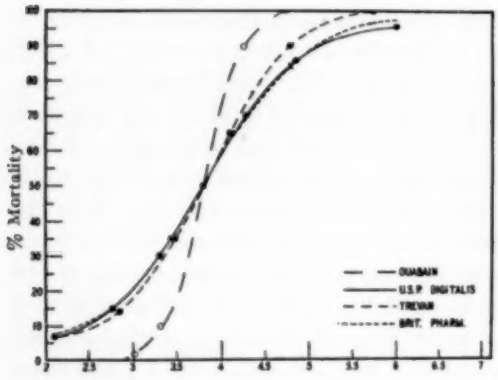


Fig. 1.

Fig. 1.—Characteristic mortality curves for frogs injected with digitalis or strophanthus—injection being made into the lymph sac. For the U. S. P. digitalis curve *Rana pipiens* was employed and the one-hour period of observation. For the ouabain curve (Chapman and Morrell) *R. pipiens* and the lethal dose method were used and for the Trevan digitalis curve *R. temporaria* and the lethal dose method. The two crosses on the U. S. P. curve indicate the mortality obtained when *R. pipiens* were used with the lethal dose method.

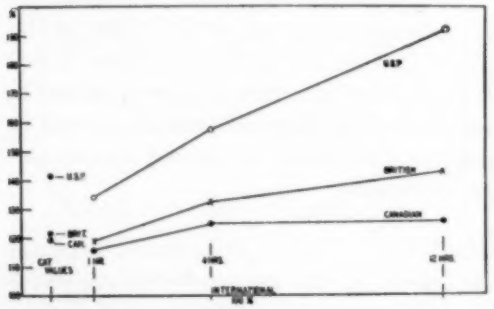
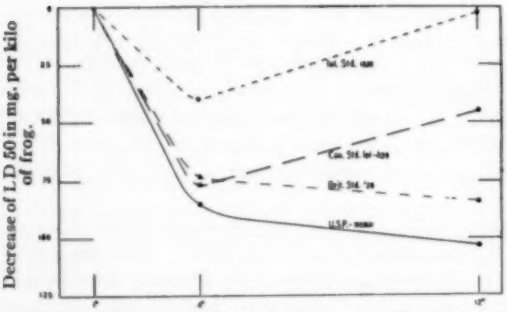


Fig. 2.

Fig. 2.—Potency of the three national standard powders of digitalis in relation to the International standard powder as determined on frogs using the one-, four- and twelve-hour period of observation. The values obtained by the cat method are indicated at the left of the curves and show how closely the cat and one-hour frog results agree.



Time in hours between injection and observation of end-points.

Fig. 3.

Fig. 3.—Curves of the four standard digitalis powders drawn on basis of decrease in M. L. D. 50, the one-hour value being taken as zero. The curves show the great decrease in dosage for the four-hour period observation with two powders still showing decreased dosage in the twelve-hour period while the Canadian and International Powders require large doses. Each of the two pairs of curves take a parallel course in the 4–12-hour period but in opposite directions.

L. D. per kilo of frog.

	U. S. P.	Brit.	Can.	Int.
One hour	391	446	470	524
Four hours	306	372	394	484
Twelve hours	288	362	425	522

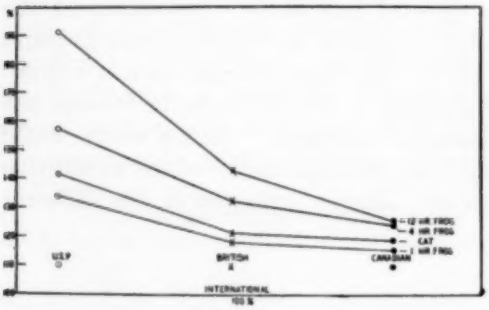


Fig. 4.

Fig. 4.—Curves showing the potency of the three National Standard digitalis powders in relation to the International Powder as determined by the cat and frog methods of assay. A considerable degree of parallelism is shown and a close approximation of results especially between the cat and one-hour frog results.

THE ASSAYS.

The assays on frogs were carried out by the official U. S. P. one-hour method; by the four-hour method as recommended by the Health Committee of the League of Nations; and by the twelve-hour period of observation (lethal dose method). The latter method was studied as it had been employed in the assay of the British and the Canadian standards and had also been used in this country by certain workers since the earliest days of biological standardization. In addition to the various modifications of the frog methods which were used, the cat method was also employed as will be described later.

For the assays on frogs the various powders were injected as tinctures. These were prepared by adding 10 cc. of 80 per cent alcohol to each gram of drug in a glass-stoppered flask and allowing the same to stand with frequent shaking at room temperature for twenty-four hours as directed in the Pharmacopœia. Before injection the alcohol content was reduced to 20 per cent by evaporation over a water-bath at a temperature not exceeding 50° C., the initial volume being restored by adding distilled water. The undiluted tinctures, when not in use, were kept in a refrigerator and no two tinctures were compared which differed in age from each other by more than a week.

In carrying out the assays upon frogs the statistical method of Trevan was employed. For this purpose it was necessary to construct a standard curve, inasmuch as the curve used by Trevan is based upon the lethal dose method using *Rana temporaria*. The curve employed by the Canadian workers, Chapman and Morrell, is also based upon a similar period of observation but uses ouabain as a standard and employs *Rana pipiens*. Accordingly, a curve was constructed in this laboratory using *Rana pipiens* and the official one-hour U. S. P. method and the new U. S. P. standard powder. The curve was constructed in a manner similar to that employed by Chapman and Morrell using 570 frogs for the purpose. The range of variation in doses of digitalis between those killing some frogs (1–5%) and those killing 100 per cent was shown by this curve to be in the ratio of about 1 to 5.00. Trevan found by the lethal dose method on *Rana temporaria* a ratio of 1 to 4.85, practically the same ratio. On the other hand, the ratio of variation in killing dosage of ouabain was found by Chapman and Morrell to be as 1 is to 1.60. In Fig. 1 (p. 292) the Trevan curve is shown superimposed upon the U. S. P. curve and it is seen that the two curves are practically identical. The Chapman and Morrell curve, also shown in Fig. 1, is much steeper than the other curves so that in its middle portion for each increasing increment in dosage the mortality percentage rises very rapidly. In order to make a further comparison possible between the U. S. P. curve and the Trevan curve, with the idea of checking the effect of using different varieties of frogs, we located the principal points for another curve using the lethal dose method with *Rana pipiens*. These points, also shown in Fig. 1, were gained by using 180 frogs, and it is seen that they coincide almost exactly with those found by the one-hour method. It would seem, therefore, that regardless of the period of observation (one-hour or lethal dose) or variety of frogs (*R. pipiens* or *temporaria*) the characteristic curve for digitalis has the same slope and that the two species of frogs display the same degree of variation to toxic doses of digitalis. (This statement holds good, at present, only for the lymph sac method of injection.) These findings would therefore seem to justify the use of the statistical method when either species of frogs is used or either period of observation (one or twelve hours) without first establishing an integrated curve in the individual laboratory. In other words, the Trevan-U. S. P. curve apparently can be used in any laboratory for the assay of digitalis when a frog lymph sac method is used. On the other hand the curve of Chapman and Morrell obtained with ouabain is much steeper than the digitalis curve and therefore it should not be used in the assay of digitalis. Chapman and Morrell have pointed out that errors due to the use of the ouabain curve for digitalis may be minimized by using doses which would bring the mortality between the 25 and 75 per cent points. It is true that this procedure would lessen the errors as the differences between the two curves are less within these limits—the deflection being much greater above and below these percentages.

In Table I are given the results of the assays of the different powders when the official U. S. P. method (one hour) is used, the tinctures employed being fresh and prepared under identical conditions and injected into the anterior lymph sacs of the frogs.

TABLE I.—ONE-HOUR FROG METHOD. USING 10 PER CENT TINCTURES OF THE DIFFERENT POWDERS PREPARED AS DESCRIBED IN THE TEXT. TWENTY FROGS WERE USED FOR EACH ASSAY.

Date, 1935.	Preparation.	Dose per Gram of Frog.	Number of Frogs Discarded.	Number of Frogs Dead.	Per Cent Mortality.	U. S. P. Curve.	Potency of Powder in Per Cent of Int. Std., 1926.
Oct. 28	Int. Std., 1926	0.006	2	12	66.6	4.18	145.1
	Int. Std., 1926	0.005	3	10	58.8	4.00	126.5
	U. S. P. 915921	0.005	1	17	89.4	5.06	...
Oct. 31	Int. Std., 1926	0.005	2	9	50.0	3.80	...
	U. S. P. 915921	0.004	1	11	57.9	3.98	130.9
Nov. 5	Int. Std., 1926	0.005	4	8	50.0	3.80	...
	U. S. P. 915921	0.004	1	11	57.9	3.98	130.9
	Brit. Std. 1928	0.0045	3	9	52.9	3.86	112.8
Nov. 6	Int. Std., 1926	0.005	2	7	38.8	3.54	...
	U. S. P. 915921	0.004	0	11	55.0	3.90	137.7
	Brit. Std., 1928	0.005	2	11	61.1	4.04	114.1
	Can. Std., 1928	0.005	0	12	60.0	4.02	114.0
Nov. 7	Int. Std., 1926	0.006	3	11	64.7	4.14	...
	Brit. Std., 1928	0.004	0	8	40.0	3.58	129.7
	Can. Std., 1928	0.004	0	6	30.0	3.32	120.3
	Can. Std., 1928	0.005	0	11	55.0	3.90	113.0

The average of these results shows that in terms of the International standard powder the three powders assayed possess potencies as follows:

International standard powder considered as	100.00%
U. S. P. powder No. 915921	134.22%
British 1928 standard	118.87%
Canadian 1928 standard	115.77%

In Table II are to be found the results obtained by assaying the same four powders by the frog method using a four-hour period of observation.

TABLE II.—FOUR-HOUR FROG METHOD. TEN PER CENT TINCTURES USED AS GIVEN IN TABLE I AND TWENTY FROGS EMPLOYED IN EACH ASSAY.

Date.	Preparation.	Dose per Gram of Frog, Cc.	Number Dead.	Per Cent Mortality.	U. S. P. Curve.	Potency of Powder in Per Cent of Int. Std., 1926.
Nov. 20	Int. Std., 1926	0.0055	15	75	4.42	...
	U. S. P. 915921	0.004	18	90	5.10	154.9
Nov. 20	Int. Std., 1926	0.005	11	55	3.90	...
	U. S. P. 915921	0.0035	13	65	4.15	152.0
Nov. 20	Int. Std., 1926	0.0045	7	35	3.45	...
	U. S. P. 915921	0.003	10	50	3.80	165.2
Nov. 30	Int. Std., 1926	0.0045	9	45	3.68	...
	Brit. Std., 1928	0.004	13	65	4.14	135.0
	Can. Std., 1928	0.004	10	50	3.8	124.5
Jan. 26	Int. Std., 1926	0.005	11	55	3.9	...
	Brit. Std., 1928	0.004	12	60	4.04	130.0
	Can. Std., 1928	0.004	11	55	3.9	125.0

From these results it appears that in terms of the International Powder the potencies of the three national standards are as follows:

International standard powder as	100.00%
U. S. P. powder No. 915921	157.37%
British 1928 standard	132.5 %
Canadian 1928 standard	124.7 %

In Table III the same powders have been assayed by the twelve-hour or lethal dose method, that being the method which was first used to assay digitalis in the latter part of last century.

TABLE III.—TWELVE-HOUR FROG (LIMITLESS) METHOD. TEN PER CENT FRESH TINCTURES USED AND TWENTY FROGS USED IN EACH ASSAY EXCEPT AS NOTED.

Date.	Preparation.	Dose per Gram of Frog, Cc.	Number Dead.	Per Cent Mortality.	U. S. P. Curve.	Potency of Powder in Per Cent of Int. Std.
Nov. 16	Int. Std., 1926	0.0045	6	30	3.32	...
	U. S. P. 915921	0.003	11	55	3.90	176.2
	U. S. P. 915921	0.0025	7	35	3.44	185.5
	Thirty Frogs Used in Each Assay.					
Nov. 19	Int. Std., 1926 (X)	0.0048	7	23.3	3.20	187.5AX 190.6AY 202.7BX
	Int. Std., 1926 (Y)	0.0053	10	33.3	3.48	205.8BY
	U. S. P. 915921 (A)	0.0028	11	36.6	3.50	...
	U. S. P. 915921 (B)	0.0033	13	76.6	4.46	...
Dec. 2	Int. Std., 1926	0.0048	6	30	3.32	...
	Brit. Std., 1928	0.004	12	60	4.04	145.2
Dec. 2	Int. Std., 1926	0.0048	6	30	3.32	...
	Can. Std., 1928	0.004	7	35	3.44	124.3
Jan. 27	Int. Std., 1926	0.0055	12	60	4.04	...
	Brit. Std., 1928	0.004	13	65	4.14	140.8
Jan. 30	Int. Std., 1926	0.0055	15	75	4.43	...
	Can. Std., 1928	0.0045	16	80	4.59	126.6

NOTE: The frogs were followed for an additional twelve hours after the designated period of twelve hours with no change in mortality statistics; hence these figures may also be considered as being derived by the so-called limitless time method.

Table III shows that by this method the following relative potency results were obtained:

International standard powder as	100.00%
U. S. P. powder No. 915921	191.4 %
British 1928 standard	143.0 %
Canadian 1928 standard	125.4 %

The figures in Tables I, II and III, indicating the relative potencies of these powders as obtained by different frog methods, are collected in Table IV and with these are given the amounts of the individual powders which would correspond in potency to 1 Gm. of the International Powder as determined by the different methods.

TABLE IV.

	U. S. P.		British.		Canadian.	
International	100.00%	1.0000	100.00%	1.0000	100.00%	1.0000
One-hour frog	134.22	0.7441	118.87	0.8419	115.77	0.8637
Four-hour frog	157.37	0.6341	132.50	0.7407	124.7	0.8019
Twelve-hour frog	191.40	0.5224	143.00	0.6993	125.4	0.7974

A comparison of these results with those obtained upon the same powders by other workers is important not only as indicating the approximate accuracy of these results but also as demon-

strating the feasibility of securing comparable results in different laboratories and indeed even when using different species of frogs. At our request Dr. Chen of Indianapolis very kindly assayed the U. S. P. powder by the U. S. P. method and reported a potency of 135% in relation with the International Powder as compared with our findings of 134.2%. Trevan and Gaddum, using *Rana temporaria* found the British powder to be 138% of the International while we, using *Rana pipiens* found it to be 143%. In each case the twelve-hour method was used. Our results differed only 5% from the British figures even though a different species of frog was used.

The Canadian powder as assayed in the Laboratory of Hygiene at Ottawa had a potency of 117.5% of the International powder, while our results gave it a potency of 122.5% when using the "O" curve used in the Canadian laboratory (or 125.4% using the U. S. P. curve), a difference again of only 5%. Also it must not be forgotten that seven years have intervened between the time the British and the Canadian workers assayed their powders and when they were assayed in this laboratory. Such comparative assays also furnish evidence as to the keeping qualities of digitalis powder when it is stored under proper conditions.

It is apparent from the results given above that the U. S. P. powder is much more potent than any of the others. This is due to the fact that it is a blend of three carefully selected specimens while the International Powder, for example, was intended to represent a good average quality product, being derived from ten different sources. It is a question whether, when the present supply of U. S. P. powder is exhausted, it would not be better to select a powder of only average strength than one which is so potent as such powders are more likely to give better comparative results than those which differ widely in potency. It is interesting to note that the new Canadian standard which has just been issued is very close to the International standard in potency.

A study of the percentage figures given in Table IV emphasizes again what others have pointed out before, *viz.*, that with different periods of observation the potencies of different powders in relation to a standard vary considerably—in general showing an indicated ascending degree of potency as the period of observation is lengthened. An important point, however, is that the lines of indicated increase for the different powders do not run parallel. For example, in this series the strongest powders show the greatest degrees of divergence from the others in the longer periods of observation (Fig. 2 (p. 292)). This is true not only for the U. S. P. powder but also for the British, while the deflection of the Canadian standard from the International is much less. Also with the Canadian powder it is seen that the greatest deviation from the International takes place in the interval between the one- and four-hour periods of observation. This lack of parallelism between the results obtained by the different methods (1-, 4-, 12-hour) disposes of the thought that possibly a definite ratio might be found in the results so that figures obtained by one method might be used as a basis for estimating the probable results to be obtained by another. For instance, if such a ratio existed a potency figure obtained by the lethal dose method might be used to calculate the potency that would be obtained by the one-hour method. These findings show that this is impossible. For example, if an unknown powder should happen to be identical with the U. S. P. powder, a twelve-hour lethal dose percentage of 191 per cent of the International would signify a one-hour figure of 134 per cent, in other words, a ratio between the two values of about three to two. On the other hand, with a weaker powder, intermediate between the U. S. P. and the International (such for example as either of the two powders herein studied) even though the twelve-hour value was known it would be impossible to calculate the one-hour value from it. There would no

longer be a ratio of three to two but with a powder reacting like the British a ratio of seven to six and with the Canadian a ratio of about twelve to eleven. It will be seen therefore that the possibilities for trouble would be considerable.

The reason for such varying relationships among these powders is not at all clear. So far as these four powders are concerned they fall into two groups—a strong group and a weaker—which in this instance is represented by the International Powder, the strength of which was based upon a mixture of ten powders obtained from different sources. The strong group is represented by the U. S. P. powder—a blend of three very carefully selected samples. It would seem reasonable to suppose that these strong powders contain a larger percentage of those glucosides which are absorbed with difficulty or at least require a longer period of time to unfold their full strength.

In order to get further light upon this question the lethal doses for 50 per cent of the frogs injected (LD50) were determined and expressed in mg. per kilo of frog, using the different periods of observation and basing the curves so obtained upon the one-hour period, considering it as zero. The other points were obtained by calculating the decrease in mg. which represent the LD50 for the different powders and observation periods. The results are shown in Fig. 3 (p. 292). The LD50 in each instance is the mean of three groups of twenty frogs each and the integrated frequency curve for digitalis was used in the correcting of the mean dosage to LD50. All determinations were made in January 1936, and for a single method they were carried out upon all the powders in a single day so as to avoid possible variations due to diurnal or seasonal influences.

The LD50 dosages for all the preparations are less for the four-hour and for the twelve-hour interval than for the one-hour period. This decrease in dosage has been noted by many workers and it holds good for digitalis, strophanthus and ouabain. In the present instance the percentage decreases for the different powders for the different observation periods are as follows:

	Four-Hour.	Twelve-Hour.
International standard 1926	7.6%	0.4%
Canadian standard No. 428	16.1	9.6
British standard, 1928	16.1	18.8
U. S. P. standard No. 915921	21.7	26.3

The curves (Fig. 3 (p. 292)) show very clearly that the greatest deviation from the one-hour figures occurs in the "one–four" hour interval and certainly lends weight to the argument which has been made that a longer period than one hour should be allowed for complete absorption. This possible source of error might not be of so much importance in the practical use of the method as it would appear at first sight, if it could be assumed that approximately equal amounts of glucosides would be absorbed in the one-hour period, which, of course, would be assuming entirely too much. However, in spite of this theoretical objection to the method it has on the whole proved satisfactory in the thirty-five years that it has been used in this country. Some further light upon this question appears later in this paper. It is certainly true, that, as shown by the findings of Dr. Chen and ourselves in the present study, accurate comparative results can be obtained by the one-hour method if attention be paid to follow carefully the essential details of the technique.

In some comparative assays which have been made, much valuable time and material have been wasted by failure to observe the fundamental directions for

carrying out the assay. For example, it is impossible to draw conclusions of any value as to the comparative potency of different products from figures gained in assays which have been carried out with no regard to temperature control. It is essential in biological assays, as in chemical assays, that in order to secure trustworthy results, care must be taken to control each factor entering into the procedure. This should be simple with the new Pharmacopœia, as it provides a powder of digitalis for the standard and the potency of the unknown is to be compared with the standard, each powder being prepared for use and injected under like conditions.

Figure 3 (p. 292) shows further that in the "four–twelve" hour period again the curves do not run parallel, in that for the U. S. P. and the British powders a further decrease in dosage is shown, while for the Canadian and International Powders the "twelve-hour" fatal dose is greater than for the four-hour period. In the case of the International Powder the LD for the twelve-hour period is practically the same as for the one-hour; 522 and 524 mg. Thus the fatal doses of two of the powders increase in the four–twelve-hour interval while the doses for the other two decrease, displaying a sharp difference of reaction between the two groups. This phenomenon accounts for the increased relative potency of the U. S. P. and British standards in comparison with the International.

Another factor which must play a part in the assays is the destruction or excretion of the glucosides during the period of observation. Such features would doubtless appear most prominently in the twelve-hour period and be seen best with the weaker powders. With such powders it is not uncommon to observe, when borderline doses have been given, that hearts which have been seen to be at a standstill at an earlier hour may again be beating at the twelfth hour. It is evident that recovery from a mild state of poisoning has taken place in the interval.

The directional change in the curve (Fig. 3 (p. 292)) for the International standard which was noted in this laboratory has also been described by Rowe who found the M. S. D. of this powder was 600 mg. per kilo by the one-hour method; M. L. D., 375 by the four-hour method and 498 mg. by the twelve-hour. Only in this powder does he have a complete series of figures for digitalis but in several instances he has comparisons of the one- and twelve-hour doses in which the twelve-hour dose was higher than the one-hour, a condition which we have not found in our studies. Finally these curves show that the main differences in the ratio among these powders in relation to the International occur in the first four hours; this difference continues to grow greater with the U. S. P. and British powders but in the case of the Canadian it runs parallel to the International—the only deviation being in the four-hour period.

To recheck the potency findings obtained, four fresh tinctures were prepared using amounts of the U. S. P. powder which our results had shown corresponded in potency to one Gm. of the International standard when tested by the different periods of observation. The amounts of powder taken, to which in each instance 10 cc. of 80% alcohol were added, were as follows:

For the standard tincture of the International Powder	1.000 Gm.
U. S. P. powder. One-hour frog method	0.7441 Gm.
U. S. P. powder. Four-hour frog method	0.6341 Gm.
U. S. P. powder. Twelve-hour frog method	0.5653 Gm.*

* The original adjusted tincture for the twelve-hour frog method was made on the basis of the early assays which had given findings which were too high. Thus 0.5653 Gm. was used instead of 0.5224 Gm. which the completed assays showed to be correct. Accordingly the final percentage found was recalculated upon the basis of the corrected figure.

Each of the three adjusted tinctures was then assayed in comparison with the International by two of us (M. and S.) working independently, comparative assays being made on the same day. In each assay twenty frogs were used and the percentage potency calculated from the mortality, using the integrated frequency curve for digitalis.

TABLE V.—ASSAY OF ADJUSTED TINCTURES—CALCULATED TO POTENCY OF 1 GRAM OF THE INTERNATIONAL POWDER AND COMPARED WITH ORIGINAL VALUES (TABLE IV).

Date.	Preparation.	Dose in Cc. per Gram Frog.	Per Cent Mortality.	Curve Number.	U. S. P. Powder in Per Cent of Internat. on Bases of 1 Gm. of Powder. Per Cent of Int. Std., 1926.	Adjusted Tincture.	Unadjusted Tincture, Table IV.
			One-Hour Frog Method.				
Dec. 10	Int. Std., 1926	0.005	40	3.57	....	....	....
Dec. 10	U. S. P.	0.005	55	3.9	109.27	146.64	....
Dec. 11	Int. Std., 1926	0.005	50	3.8	.. .	....	....
Dec. 11	U. S. P.	0.005	55	3.9	102.62	137.77	....
				Mean	105.94	142.21	134.22
			Four-Hour Frog Method.				
Dec. 11	Int. Std., 1926	0.005	65	4.12	...	....	....
Dec. 11	U. S. P.	0.005	60	4.02	97.1	153.12	157.37
			Twelve-Hour Frog Method.				
Mar. 20	Int. Std., 1926	0.0055	20	3.18	...	....	....
Mar. 20	U. S. P.	0.0055	40	3.54	112.2	....	....
Mar. 21	Int. Std., 1926	0.0055	40	3.57	...	....	....
Mar. 21	U. S. P.	0.0055	50	3.8	106.4	....	....
		Mean on basis of 0.5653 Gm.			109.3		
		Recalculated on basis of 0.5224 Gm. and on basis 1 Gm. powder			101	193.3	191.4

The potencies of these adjusted tinctures should theoretically have been found to be of 100 per cent strength, barring errors inevitable in any bioassay; and a survey of the findings in Column six shows that they all do in fact fall within six per cent of the theoretical 100 per cent. The findings on the adjusted tinctures were then recalculated on the basis of the use of 1 Gm. of powder in each case and these figures given in Column seven may be compared with the original findings (Table IV) as recorded in Column eight. These results obtained with tinctures using quite different amounts of powdered drug and carried out with a different lot of frogs at different times of the year show a maximum variation of 8 per cent and a minimum difference of 2 per cent, all well within the limits of error allowable in the biological method of assay.

A study of Table V giving the results obtained with the adjusted tinctures confirms the earlier findings as to quantitative differences in the potency relationship obtained by the different methods with the four powders. Age of the powder apparently does not play any conspicuous part, as the British and International are almost the same age and yet they act quite differently, the British 1928 acting like the U. S. P. of 1935 and not like the Canadian which was adopted in the same year as the British (1928).

Finally it may be said that these studies have been carried out with a considerable degree of completeness, as it is with such methods of assay that the manufacturer is concerned when he uses the U. S. P. powder in testing his products.

ASSAY OF STANDARD DIGITALIS POWDERS ON CATS.

In a continuation of this study all the digitalis powders were assayed by the cat method using the Magnus modification of the original procedure in which the drug is injected in the form of a dilute infusion. These infusions were made in one-half per cent strength keeping them upon a water-bath for fifteen minutes according to the directions in the Dutch Pharmacopœia. They were always used fresh, in no case more than six hours after they had been prepared. During the course of the work certain changes in technique were made leading to greater accuracy in results. The most important of these was the adoption of a certain definite period of time during which the drug was injected resulting in death of the animal. The time period chosen was forty minutes being intermediate between the thirty- and fifty-five-minute interval which is in common use. The variation in length of the interval was rarely more than a minute or two.

The infusions were injected at a uniform rate by means of an electrically driven pump, the speed of injection being varied to conform to the weight of the cat and the strength of the powder by changing the length of the stroke of the piston. The rate of injection was determined from the results obtained upon the first three cats. In the first cat, 5 mg. of the drug (1.0 cc. of 0.5% infusion) were administered per minute. From these findings the lethal dose for the cat was calculated and to the next two cats this amount was administered at such a rate that it should kill in forty minutes. From the results thus obtained on the three cats the average fatal dose per kilo was computed and injected into the other animals in the required time of forty minutes, the amount to be actually injected being adjusted according to weight of the individual cat. All the cats were anæsthetized with urethane, one Gm. per kilo given intraperitoneally, in the form of a freshly prepared fifty per cent solution. Artificial respiration was used throughout and blood pressures were taken, the final reading of the amount of infusion needed to kill being taken when the pressure fell to zero and no sign of heart activity was present.

All series of tests were conducted on a sufficiently large number of cats so that the average of the deviations of individual lethal doses from the mean, expressed in per cent of the mean, was less than $6.67\sqrt{n-1}$. The results of the assays upon cats of the four powders are given in Table VI.

TABLE VI.—ASSAY ON CATS OF THE THREE NATIONAL STANDARD DIGITALIS POWDERS IN TERMS OF POTENCY OF THE INTERNATIONAL POWDER.

Preparation.	Anæsthetic.	Number of Cats.	Mean Weight of Cats.	Calculated Duration of Assay.	Actual Mean Injection Time.	Mean Fatal Dose; Mg. per Kilo.	Per Cent of Intrnl. Std., 1926.	S. D. of Mean (M.E.).	$6.67\sqrt{n-1}$ Deviation Allowed.	$6.67\sqrt{n-1}$ Actual Deviation.
Intnl. Std., 1926	Urethane	17	2.4	40′	38′	110.35	....	2.3	27.43%	5.9 %
U. S. P. 915921	Urethane	24	2.42	40′	37′	77.90	141.65	1.53	32.66%	7.67%
Intnl. Std., 1926	Ether	6	2.13	40′	38.1′	93.0	....	2.93	16.3%	5.15%
U. S. P. 915921	Ether	7	2.28	40′	37.4′	64.96	143.0	2.47	16.3%	8.20%
Brit. Std., 1928	Urethane	7	2.42	40′	41′	90.75	121.60	3.25	16.3%	6.92%
Can. Std., 1928 No. 428	Urethane	7	2.35	40′	40′	92.53	119.26	3.275	16.3%	7.05%
Intnl. Std., 1926	Urethane	5	2.06	55′	55′	93.4	....	5.9	13.34%	11.45%
U. S. P. 915921	Urethane	7	2.31	55′	56.3′	66.1	141.3	3.4	16.3%	11.7 %

In the assay of the International standard powder when a sufficient number (17) of cats had been used so as to give a fair idea of its potency it was found that the average lethal dose was 110.35 mg. per kilo of cat weight. This was very different from the original value of 89.7 mg. found in Utrecht in 1926. This marked discrepancy of over 20 mg. per kilo would certainly indicate deterioration of the powder unless some other explanation could be found for it. Inasmuch as we were using urethane as an anæsthetic, whereas the original assays were made using ether, a number of additional assays (6) were made in which ether was substituted for the urethane. Under these conditions an average dose of 93 mg. per kilo was found. According to this the etherized animals required only 84 per cent as much drug as did the urethanized animals. But, as the table shows, the potency of the U. S. P. powder was found to be 141.65 per cent of the International when urethane was used and 143.3 per cent when ether was employed, the results being practically identical. These facts being established, the remaining powders were all assayed using urethane on account of the ease of its administration and the uniformity of the degree of anæsthesia.

The results obtained in the present study when using ether, therefore, were practically the same (93 mg.) as those found at Utrecht in 1926 (89.7 mg.) and are important in that they indicate the excellent keeping qualities of powdered digitalis when stored under proper conditions. They also demonstrate the possibility of getting comparable results when comparable methods are employed, and above all, the absolute necessity of securing such identical or comparable conditions. If these factors are controlled it is possible, probably, to vary the conditions somewhat if the same deviation in method is followed with both powders to be assayed and yet to obtain comparable results.

A very important point in connection with these studies is brought out by a comparison of the results obtained with cats and by the various frog methods. One argument which has been made for the cat method is that the cat biologically is much closer to man than is the frog and therefore is much more suitable as a test animal for the assay of drugs which are to be administered to man. Such an argument is, of course, hard to contradict. Another advantage which is urged in favor of the cat method is, that here, the drug being injected intravenously, there is no question as to its absorption as there is in the case of the lymph sac injection into frogs. For these reasons a comparison of the results obtained on frogs with those gained on cats is especially interesting. Such comparative figures are given in Table VII based on the International Powder considered as 100 per cent. The comparative results are also shown in Fig. 2 (p. 292).

TABLE VII.—PERCENTAGE POTENCY OF STANDARD POWDERS IN TERMS OF INTERNATIONAL STANDARD (1926) AS 100%.

Method.	U. S. P. Powder.	British.	Canadian.
Cat	141.65%	121.60%	119.26%
One-hour frog	134.22	118.87	115.77
Four-hour frog	157.37	132.50	124.70
Twelve-hour frog	191.40	143.00	125.40

A study of these results shows that the cat method and the one-hour frog method yield results which are remarkably close, differing in the case of the U. S. P. Powder by 7%; the British 3% and the Canadian 3.5%. On the other hand the four- and the twelve-hour results differ much more widely from the cat results indicating that in spite of the short period of observation and other theoretical objections the results by the one-hour method agree well with those obtained with cats.

It is worthy of note that the British workers found for their standard (by the

etherized cat method) a potency, relative to the International standard, of 116% while we found 121.6%; and by the twelve-hour frog (*R. temporaria*) the British report a potency of 138% as compared with our findings (*R. pipiens*) of 143%. Such checking and cross-checking demonstrate anew the accuracy attainable by biological methods. The figures giving the relative potency of the Canadian powder again demonstrate that it reacts in a manner very similar to the International Powder which it approaches in potency more closely than do the other powders and the assay results obtained upon it by all the four methods do not differ more than about 10 per cent.

In order to check this relationship still further a tincture was prepared from the U. S. P. powder, using the amount indicated by its potency in relation to the International standard, as determined by the cat method, *viz.*, 0.7060 Gm. in 10 cc. of 80% alcohol. This tincture was assayed by the various frog methods in order to see which frog value would approach most closely the theoretical potency indicated by the cat assay.

TABLE VIII.—ASSAY ON FROGS, USING THE 1-, 4- AND 12-HOUR PERIODS OF OBSERVATION, OF A TINCTURE OF THE U. S. P. POWDER OF A STRENGTH AS DETERMINED BY ITS ASSAY ON CATS.

Date.	Preparation.	Amount of Powder.	Dose in Cc. per Gram of Frog.	Mortality.	Per Cent Mortality.	Curve.	Per Cent of Int. Std., 1926.	Per Cent of Int. Std. on Bases of 1 Gm. of Powder.	Per Cent of Int. Std. on Basis of Unadjusted Tincture, Table IV.
			One-Hour Frog Method.						
12/10	Int. Std.	1 Gm.	0.005	8	40	3.57	....	....	....
12/10	U. S. P.	0.7060	0.005	7	35	3.45	96.64	136.79	134.24
			Four-Hour Frog Method.						
11/29	Int. Std.	1 Gm.	0.005	14	70	4.28	....	....	....
11/29	U. S. P.	0.7060	0.005	16	80	4.6	107.47	....	....
11/30	Int. Std.	1 Gm.	0.0048	9	45	3.69	....	....	....
11/30	U. S. P.	0.7060	0.0048	11	55	3.9	105.70	....	....
						Mean	106.59	150.98	157.7
			Twelve-Hour Frog Method.						
12/2	Int. Std.	1 Gm.	0.0048	6	30	3.32	....	....	....
12/2	U. S. P.	0.7060	0.0048	13	65	4.14	124.7	176.6	191.4

Here again the close relationship between the potency findings as determined by the cat and the one-hour frog methods is clearly shown, a difference of only 2.5% being present, against a 7% difference by the four-hour method and 15% by the lethal dose method.

Rate of Injection.—An important point in the assay of digitalis by the cat method, and one to which reference was made earlier, is the effect of varying the rate of injection upon the potency figures. To study this feature further we compared the results of injecting infusions of two of the powders at a slower rate than we had used in the earlier assays, taking 55 minutes in place of our average of 38 minutes and using five cats for the International powder and seven for the U. S. P.

The following table gives the results obtained by the two rates of injection.

TABLE IX.—EFFECT OF VARYING THE RATE OF INJECTION OF THE DIGITALIS INFUSION UPON THE ABSOLUTE AND RELATIVE TOXICITY OF THE DRUG IN THE CAT.

	Period of Injection—55 Min.		Period of Injection—38 Min.	
	Mean Mg. per Kilo.	Per Cent of International.	Mean Mg. per Kilo.	Per Cent of International.
International	93.4	...	110.35	....
U. S. P. Powder	66.1	143.3	77.90	141.65

Here again, as in the case of the figures obtained using different anæsthetics, the individual absolute results for the two rates of injection are entirely different but when comparative assays are made, under like conditions, the percentage potency ratios at the two rates are again practically identical. From the theoretical standpoint it might have been supposed that with the longer period of injection larger amounts of the drug would be tolerated than when it was administered more rapidly, but, as a matter of fact, in each instance it took 18 per cent more drug to kill in 38 minutes than it did in 55 minutes indicating that with the longer period the drug has a better opportunity to unfold its full activity and therefore the smaller dose is toxic. From this it might be thought that the longer period is to be preferred, but when the final calculations are made the comparative percentage results are identical. These findings explain the favorable results obtained by the one-hour frog method in comparison with the longer periods of observation, in that, while the longer period gives greater opportunity for absorption, apparently comparable degrees of absorption occur in the shorter period. An objection which may very properly be made to the use of the prolonged period of injection, at least, in so far as our experience goes, is that the individual variation of the experimental animals increases as the period is lengthened. This is shown by the relatively high average of the deviations of the L. D. from the mean which is expressed in per cent of the mean L. D.

In view of the fact that a prolongation of fifteen minutes in the time of injection makes such a difference in the toxic dose of digitalis, certainly a more exact time limit for the injection should be adopted than one varying anywhere between thirty and fifty-five minutes or even ninety minutes as some advocate. It also demonstrates how indefinite is the term "cat unit." This term is employed to denote the amount of digitalis which will prove fatal to the cat calculated as per kilo of body weight when the drug is injected under standard conditions. But as we have shown, the absolute amount of drug necessary to kill a certain weight of cat means little, as the fatal dose will vary depending upon the rate of injection of the drug and upon the anæsthetic employed. Where ether is used the fatal dose, and therefore the "cat unit," is much smaller than where urethane is employed. Our results have also been confirmed and the general subject reviewed very recently by Haskell.[1] In his experiments he found that with cats anæsthetized with ether digitalis proved fatal in doses much smaller than when the animals were given dial-urethane.

It would seem necessary to emphasize again the effect of the type of anæsthetic employed upon the toxic dose of digitalis for cats and therefore upon the quantity of drug in a "cat unit." In recent published directions for the carrying out of the assay it is said that "light ether may be used or local anæsthesia—one per cent procaine or ten per cent phenol rubbed into the skin." Since ether, urethane, dial and a variety of other anæsthetics discussed by Haskell affect the size of the toxic dose of digitalis, it may well be questioned what effect procaine or phenol would have. With very little doubt the toxic dose when ether is used would hardly be comparable to that when procaine or phenol is employed.

Since there is this deviation in indicated potency depending upon anæsthetic and rate of injection, there will always be discrepancies in results as obtained by

[1] Haskell, *J. Pharm. and Exp. Therap.*, 58, 111 (1936).

different assayists when potency is indicated in cubic centimeters or milligrams per kilo of cat weight. On the other hand, comparisons of the unknown powder with a standard preparation, both assays being carried out under standard conditions, will remove the difficulty of expressing and comparing results. The new Pharmacopœia provides for such a comparison by directing that "Powdered Digitalis" shall be of such strength that 0.1 Gm. shall possess a potency equivalent to 1 U. S. P. unit which in turn is equal in potency to one International unit, that being the potency contained in 0.1 Gm. of the International Powder.

Basing the calculations upon the figures which have been given in Table VI the number of units in the U. S. P. powder, as determined by the different variations in the cat method, is as follows:

TABLE X.

Anæsthetic.	Injection Time.	L. D. in Mg. per Kilo.		L. D. of U. S. P. Powder Calculated to Potency of 100 Mg.	Digitalis Units in 1 Gm.
		Internatl.	U. S. P.	Internatl.	U. S. P. Powder.
Urethane	35 min.	110.35	77.9	70.59	14.16
Ether	35 min.	93.0	64.96	69.85	14.31
Urethane	55 min.	93.4	66.1	70.77	14.13
					Mean 14.2

Thus by the cat method the U. S. P. powder contains 14.2 digitalis units in each Gm. and by the one-hour frog method 13.42 digitalis units.

Having established the relative potencies of the four powders both by the cat and by the three frog methods, it became a matter of interest to see whether any definite ratio or parallelism could be demonstrated between the results obtained on the two species of animals. Various efforts have been made to establish such a relationship; however, in general they have not been very successful. In spite of this failure, some still hold that some close correlation should exist between the various sets of toxicity figures. Such a comparison can be made in the present instance by comparing the results we have obtained with those reported by the English workers when their own standard was being prepared. These figures are given in the following table.

TABLE XI.—COMPARISON OF POTENCY OF BRITISH STANDARD POWDER IN TERMS OF INTERNATIONAL STANDARD AS DETERMINED IN ENGLAND IN 1928 AND IN THIS COUNTRY IN 1936.

	British Findings.	U. S. A. Findings.
12-hour frog	138%	143.0%
Cat method	116%	121.6%
Cat figures in per cent of frog figures	84%	85.0%

The results are seen to be practically identical, showing that compared with the International Powder the British and the U. S. P. powders display by the cat method a potency of 85 per cent of that shown by the frog method. We realize that these figures are too few to state that such a relationship would always exist. Our own figures do indeed demonstrate a considerable degree of parallelism between the potency findings on the three powders assayed by the different methods. As the curves given in Fig. 4, p. 292 show, the most complete agreement is again to be found between the cat and the one-hour frog methods. The greatest discrepancy is in the twelve-hour result with the U. S. P. powder. This discrepancy lessens rapidly through the weaker British powder to approach most nearly the findings obtained by the other methods in the case of the one-hour result for the Canadian powder.

In an earlier study (1929) carried out upon strophanthus six tinctures were assayed by different methods and a similar parallelism was shown to exist. However, in that study the cat values were about 30 per cent lower than the one-hour frog values—exactly the reverse of the findings with digitalis in the present work.

The British Pharmacopœia permits, in case some other method of assay than the twelve-hour frog or cat method is used, that an amount of powder be employed which is an average between the values obtained by the two methods mentioned. Thus by the frog method their powder has a potency of 13.8 units per Gm., and by the cat method 11.6 units per Gm. However, if other methods are employed, an average of these two figures or 12.7 units is considered to be close enough for practical purposes. It is of interest to see how such a rule would work if it were followed in the case of these powders for which we have definite figures of potency.

TABLE XII.

	U. S. P.		British.		Canadian.	
	Potency.	Units per Gram.	Potency.	Units per Gram.	Potency.	Units per Gram.
Average of cat and 12-hour frog figures allowed by British Pharmacopœia	166%	16.6	133%	13.3	122%	12.2
Our findings by 1-hour frog method	134%	13.4	119%	11.9	116%	11.6
Our findings by 4-hour frog method	158%	15.8	135%	13.5	125%	12.5

These figures, showing values which would be permitted under the rule adopted in the British Pharmacopœia and the actual results we obtained in the assay of the three powders show what a large discrepancy would occur if the British rule were used in the case of a strong powder such as the U. S. P. specimen. An error of almost 20 per cent would be at once introduced in adopting an "average" value and using the one-hour frog method. The error would be over 10 per cent in the case of the British powder, while in the case of the Canadian powder it is perhaps not so serious. In bioassays a certain degree of error is perhaps unavoidable but, if to this unavoidable error an initial error of 20 per cent is added, the discrepancy may be very considerable. Such an initial error would be especially important in the case of the one-hour frog method, as this method yields results which approach more closely those given by the cat method than do the four- or twelve-hour methods.

SUMMARY.

An integrated mortality curve for the assay of digitalis by the one-hour frog method was found to agree substantially with the curve obtained by Trevan using the lethal dose method. By means of the statistical method the potency of the U. S. P., British and Canadian standard powders was studied in relation to the International standard. The results showed that these powders stood in relative potency to the International as follows, in order of decreasing potency: U. S. P., British, Canadian. The twelve-hour frog method gave the highest relative potency and the one-hour the lowest, the four-hour being intermediate. Tinctures made up of various strengths, based upon the values obtained in the above assays, were assayed by the different methods and yielded figures which were strictly comparable within the limits of error.

The same powders were assayed by the Magnus modification of the cat method. The relative values obtained by this method coincided quite closely with those obtained by the one-hour frog method.

The effects of anæsthetic and rate of injection of the drug were studied and were found to have a marked influence upon the amount of drug required to kill and therefore upon the amount of drug in a "cat unit." Such discrepancies can only be avoided by the adoption of some uniform method of technique or by the use of a standard powder of digitalis with which to compare the unknown. Such a standard, based upon the potency of the International standard, is provided by the U. S. Pharmacopœia of 1936.

A CHEMICAL AND PHARMACOLOGICAL STUDY OF PHYTOLACCA AMERICANA, N. F.*

BY SAMUEL W. GOLDSTEIN,[1] GLENN L. JENKINS[2] AND MARVIN R. THOMPSON.[3]

A concise record of results obtained by previous workers on poke root (*Phytolacca Americana*, Linné) appeared in an earlier publication by Jenkins (1). The present work was carried out in an effort to clarify the uncertainties existing with reference to the chemical constituents of poke root, especially with respect to the presence of alkaloids, and the pharmacological action of the drug.

EXPERIMENTAL.

Using U. S. P. X procedures, the following constants were determined: Moisture content 9.0% and 9.3%; ash content 10.83% and 10.78%, of which 94.18% and 93.81%, respectively, was acid-soluble; crude fiber 16.10% and 16.31%; total ether-soluble extractive 0.98% and 0.985%; volatile ether-soluble extractive 0.13% and 0.15%; non-volatile ether-soluble extractive 0.85% and 0.835%; alcohol-soluble extractive 1.78% and 1.75%; diluted alcohol-soluble extractive 12.08% and 12.14%; water-soluble extractive 13.18% and 13.24%; benzin-soluble extractive 0.45% and 0.53%.

Preliminary Tests.—Tests for the presence of alkaloid gave the following results: An extract of the powdered root was obtained with Prolius fluid. The extract was shaken with 2% sulfuric acid, the aqueous layer was separated and tested with Mayer's reagent, phosphomolybdic acid, phosphotungstic acid, gold chloride and iodine test solutions. Negative results were obtained in all cases.

A chloroform extract of a dried mixture of powered root and slaked lime was evaporated and the residue was treated with 2% sulfuric acid. The aqueous solution gave amorphous precipitates with phosphomolybdic acid and phosphotungstic acid test solutions.

The procedure by which Preston (2) obtained his "phytolaccine" was repeated five times, using fresh and dried, purchased and collected poke root, without confirming his results.

The fractionation method for the separation of alkaloids as given by Thompson (3) was carried out. The tartaric acid shakings, which would certainly contain any alkaloids present in the drug gave no precipitate with Mayer's reagent and only a very slight amorphous precipitate with phosphomolybdic acid solution. The aqueous solution showed no activity when tested pharmacologically.

Separation of Starch.—The expressed juice from 200 Gm. of fresh drug deposited a white substance, which appeared to be granular when examined microscopically. The substance turned blue when treated with iodine solution, and the blue color was removed on addition of sodium thiosulfate solution. The substance gave a positive Molisch test and reduced Fehling's solution only after boiling with acid. The substance was thus identified as a starch.

Volatile Constituents.—Steam distillation of a concentrated alcoholic extract from 2.8 Kg. of powdered root yielded 1.35 Gm. of an oily substance after extraction of the distillate with ether, drying and removing the ether. The yellowish brown substance possessed a disagreeable and penetrating odor, and, when diluted, it resembled the odor of the plant. It had a sharp, pungent taste. Its specific gravity was 0.9977 23°/4° C. The high specific gravity indicated the absence of terpenes (4). A cloudy suspension was formed on mixing with 98% alcohol. This behavior is anomalous to that of the essential oils which are miscible in 98% alcohol. The oily substance may have been composed mainly of lower fatty acids and their esters.

---

* Scientific Section, A. PH. A., Dallas meeting, 1936.

[1] Abstracted in part from a thesis submitted by Samuel W. Goldstein to the Graduate School of the University of Maryland in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Professor of Pharmaceutical Chemistry, School of Pharmacy, University of Maryland.

[3] Professor of Pharmacology, School of Pharmacy, University of Maryland.

ALCOHOLIC EXTRACTIVES.

An alcoholic extract representing 5 Kg. of powdered root was mixed with slaked lime and extracted with a mixture of ether and chloroform (3:1) and then with chloroform. The ethereal solutions were combined, concentrated without heat and extracted with 2% sulfuric acid. The acid solution was made basic with ammonia water (10%) and then was extracted with ether. The ether was removed and the residue, which consisted of a clear yellow, semi-solid substance with crystals dispersed in it, gave amorphous precipitates with phosphomolybdic acid and phosphotungstic acid solutions. Attempts to separate the semi-solid from the crystalline matter by means of solvents and with chemical reagents were unsuccessful. The mixture was insoluble in petroleum benzin (b. p. 35–40° C.); soluble in anhydrous ether and absolute alcohol.

The results reported immediately above were inconclusive, but they were not in agreement with the other results obtained, inasmuch as they seemed to indicate the possible presence rather than the absence of alkaloid. In order to clarify this point, the following experiment was carried out. Twenty cc. of a hydroalcoholic (1:1) extract of poke root (1 cc. representing 1 Gm. of drug) was diluted with 20 cc. of distilled water, shaken with 75 cc. of chloroform in a separatory funnel and the chloroform layer was removed. Two cc. of the chloroform solution was tested in the usual manner with phosphomolybdic acid solution. The precipitate which formed appeared to be similar to the precipitates obtained in all the other experiments where positive tests were given by the same reagent. The remainder of the chloroform solution was evaporated to 5 cc., 4.596 cc. of $N/1$ sulfuric acid was added and the mixture was heated until all the chloroform had been removed. The aqueous residue required 4.708 cc. of $N/1$ sodium hydroxide for neutralization (methyl red indicator). This was 0.112 cc. more than the amount of $N/1$ sodium hydroxide necessary to neutralize the added acid.

The liquid remaining in the separatory funnel after the removal of the chloroform layer was made basic with ammonia water (10%) and was extracted several times with chloroform. The combined chloroform shakings (100 cc.) were extracted several times with approximately $N/1$ sulfuric acid. The acid solution gave a precipitate when tested with phosphomolybdic acid solution. The combined aqueous solution was made basic with ammonia water (10%) and was extracted with several portions of chloroform. The combined chloroform solution (100 cc.) was evaporated to 5 cc., 4.596 cc. of $N/1$ sulfuric acid was added and the mixture was heated until no chloroform remained. The aqueous residue required 4.563 cc. of $N/1$ sodium hydroxide for neutralization. This was 0.033 cc. less than the amount of $N/1$ sodium hydroxide required to neutralize the added acid. A blank determination required 0.012 cc. of $N/1$ sodium hydroxide less than the amount required to neutralize the added acid.

The above results show that the substance which is soluble in chloroform, 2% sulfuric acid and dilute alcohol, and which gives positive tests with phosphomolybdic acid solution, which has been found to be the most sensitive of the so-called alkaloidal precipitating agents used in this study, does not exhibit basic properties and is, almost certainly, not an alkaloid.

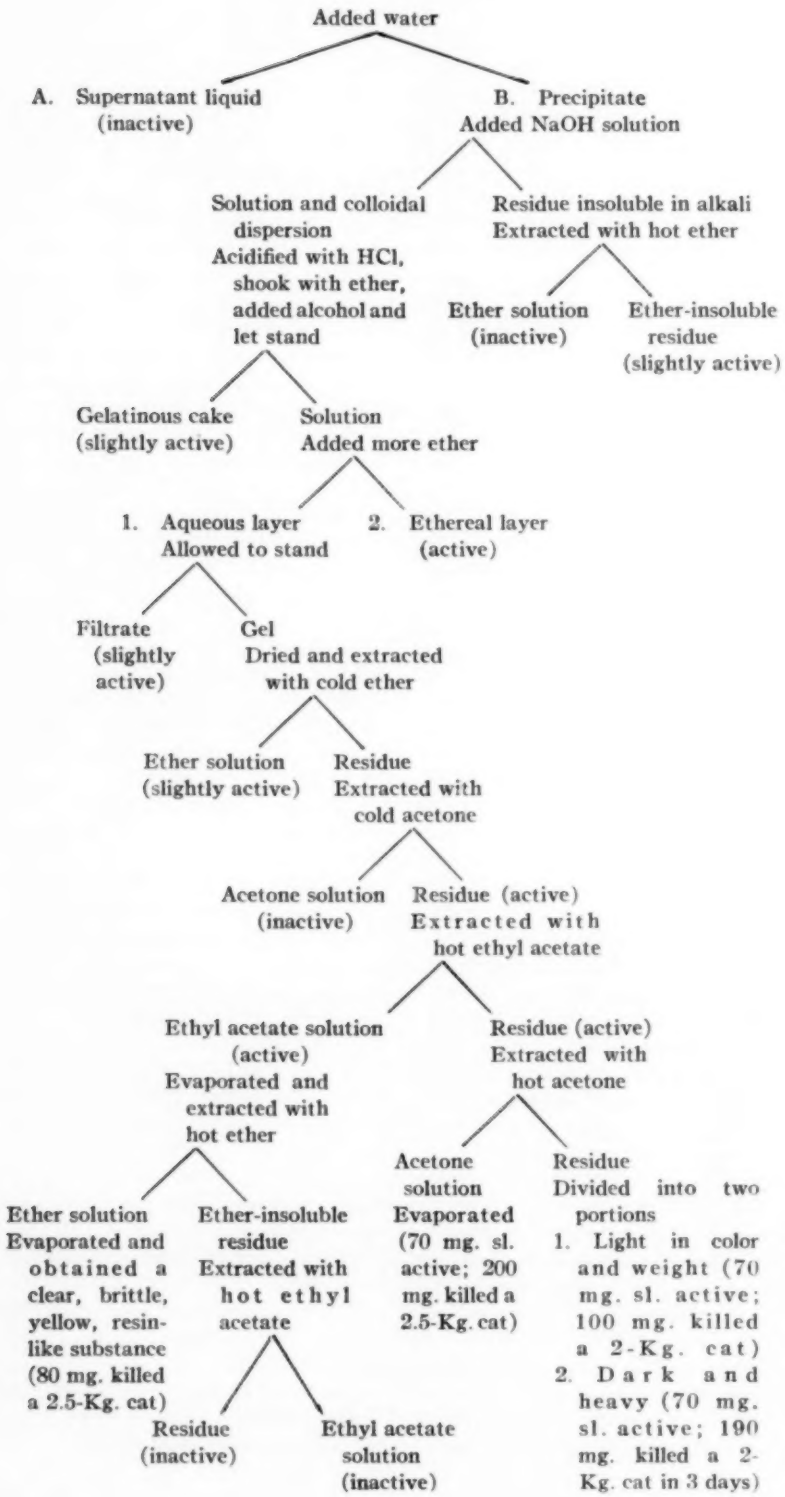
An alcoholic extract representing 11 Kg. of powdered root was concentrated without heat and the syrupy mass was mixed with water. A water-soluble fraction (A) and a water-insoluble fraction (B) were obtained.

Fraction (A), which was quite acid, was made basic with potassium bicarbonate and was extracted with ether, amyl alcohol and chloroform, respectively. The ether and amyl alcohol solution were extracted with 1% tartaric acid, the acid solutions were combined, made basic with sodium bicarbonate and extracted with ether. Removal of the ether left a pale yellowish brown, resin-like substance, part of which was dissolved in alcohol (*a*). The remainder was treated with distilled water to form solution (*b*). Both solutions formed amorphous precipitates when treated with phosphomolybdic acid and phosphotungstic acid solutions.

The chloroform solution was extracted with 1% tartaric acid until the shakings no longer gave a precipitate with phosphomolybdic acid solution. The residual chloroform solution still gave a positive test with phosphomolybdic acid solution, indicating that more than one substance in the original chloroform solution formed precipitates with the reagent. The chloroform was evaporated and the residue was dissolved in alcohol (*c*).

Solutions (*a*), (*b*) and (*c*) were tested on normal cats by injecting 5 cc., representing the water-soluble portion of the alcoholic extract of 5 Kg. of drug, of each solution intraperitoneally. In all cases the cats remained apparently normal. (*Continued on page 309.*)

Alcoholic Extractive II.


Added water
A. Supernatant liquid (inactive)
B. Precipitate Added NaOH solution
Solution and colloidal dispersion Acidified with HCl, shook with ether, added alcohol and let stand
Residue insoluble in alkali Extracted with hot ether
Ether solution (inactive)
Ether-insoluble residue (slightly active)
Gelatinous cake (slightly active)
Solution Added more ether
1. Aqueous layer Allowed to stand
2. Ethereal layer (active)
Filtrate (slightly active)
Gel Dried and extracted with cold ether
Ether solution (slightly active)
Residue Extracted with cold acetone
Acetone solution (inactive)
Residue (active) Extracted with hot ethyl acetate
Ethyl acetate solution (active) Evaporated and extracted with hot ether
Residue (active) Extracted with hot acetone
Ether solution Evaporated and obtained a clear, brittle, yellow, resin-like substance (80 mg. killed a 2.5-Kg. cat)
Ether-insoluble residue Extracted with hot ethyl acetate
Acetone solution Evaporated (70 mg. sl. active; 200 mg. killed a 2.5-Kg. cat)
Residue Divided into two portions
1. Light in color and weight (70 mg. sl. active; 100 mg. killed a 2-Kg. cat)
2. Dark and heavy (70 mg. sl. active; 190 mg. killed a 2-Kg. cat in 3 days)
Residue (inactive)
Ethyl acetate solution (inactive)

Evidently the substances obtained by extraction methods commonly used to isolate alkaloids, and which give amorphous precipitates with certain precipitating agents, are not responsible for the toxicity of poke root; especially since it was repeatedly demonstrated that suitable extracts, representing less than 5 Gm. of the same lot of drug, invariably produced death in cats weighing 2 to 3 Kg.

The aqueous solution (A), remaining after extraction with ether, amyl alcohol and chloroform, was tested by injecting 6 cc. of the solution, representing about 60 Gm. of root, intraperitoneally into a cat. The animal remained apparently normal.

Fraction (B). One-half of the water-insoluble portion of the alcoholic extract, representing 5.5 Kg. of powdered root, was treated according to the scheme on page 308.

The toxic resin-like substance, obtained according to the foregoing procedure, possessed neither alkaloidal nor glycosidal properties.

PHARMACOLOGICAL TESTS.

The pharmacological tests, by which the toxic principle was traced in the various fractionations, consisted of the parenteral administration of the extracts or fractions of the drug to cats. The intraperitoneal route was used in the majority of the tests, the end-point involving death of the animal. It was the most toxic principle of the drug, therefore, which was followed by this test in the fractionation procedure. Consequently, the entire procedure does not preclude the possibility of the existence of other undetected active but less toxic principles in the drug.

When intraperitoneal doses of 1.0 cc. per Kg. of a hydroalcoholic extract, representing 1.0 Gm. of the root per Kg., or fractions containing an equivalent amount of the toxic principle, were administered to cats, a characteristically uniform symptomatology developed. During the first half hour after receiving the drug, early symptoms of discomfort gave way to retching and, not infrequently, emesis (vomiting did not occur in all cases, especially when the purified principle was given). The animal then gradually lost the use of the hind legs and later the front legs; stupor, somnolence and a diminished perception of pain following in order. After the development of profound narcosis, the heart rate gradually became slower, the beat weaker and respiration became shallower, with ultimate death from respiratory failure.

Although these pharmacological experiments must be regarded as of a preliminary nature only, the symptomatology thus induced in normal cats by toxic doses of the resin-like principle is strongly indicative that the main site of action of this toxic substance is the cerebro-spinal axis, and that this action consists principally of an ascending depression involving both sensory and motor pathways, ultimately involving the medullary centers to cause death.

That the water-insoluble resin-like toxic principle described above is not the only constituent of the drug exhibiting pharmacological activity was shown by two noteworthy observations. Aqueous extracts of the root not containing the resin-like principle, when applied with friction to the intact human skin, produced marked irritation. Such aqueous extracts, when injected into cats, produced emesis, retching, sneezing, etc., but the cerebro-spinal depression characteristic of the resin-like principle was not produced.

Another significant observation involving humans lends itself to similar interpretation. In the milling of a portion of the root, two students, so engaged,

unwisely subjected themselves to accidental inhalation of the drug dust. Both developed very severe respiratory irritation and gastro-enteritis, one individual requiring hospitalization. More than 25 occupants of the six floors of the same building developed similar symptoms of varying degrees of severity, a considerable number being forced to discontinue their occupations for several days. The symptoms were similar to those of a severe cold associated with rhinitis and gastro-enteritis. It is important to note that no symptoms of cerebro-spinal depression developed in any case, thus indicating rather clearly that the offending principle was the water-soluble irritant substance and not the toxic, narcotic resin-like principle.

Further pharmacological study is in progress to prove or disprove the validity of the interpretations of the preliminary experiments described herein.

The fixed oil, occurring to the extent of 0.044% in the lot of drug under investigation, proved to be pharmacologically inert when administered intraperitoneally to cats in doses as high as 2.0 cc. per Kg.

The account of the chemistry and pharmacology of the drug by Solis-Cohen and Githens (5) receives considerable confirmation from the observations here reported.

AQUEOUS EXTRACTIVES.

A decoction was prepared from 300 Gm. of powdered root, and the product was treated with basic lead acetate solution, the lead precipitate being separated by filtering with suction.

Isolation of Hemicellulose.—The filtrate was treated with hydrogen sulfide gas to remove excess lead, the mixture was filtered, the precipitate was washed and the filtrate and washings were combined and allowed to evaporate without heat. The amber-colored residue consisted mainly of inorganic matter with a large amount of potassium salts. The alcoholic liquid was acidified with 2% sulfuric acid, and the white amorphous precipitate which formed was removed. The precipitated substance was insoluble in water, alcohol, ether and acetone; it was soluble in potassium hydroxide solution from which solution it was reprecipitated upon addition of acid. The substance reduced Fehling's solution, and the liquid resulting from boiling the substance with diluted sulfuric acid gave a positive test for carbohydrate with Molisch's reagent.

From the above behavior, it was concluded that the substance was a hemicellulose (6) which was liberated upon treatment with sulfuric acid. Yield: 2 Gm., representing 0.66% of the weight of the drug used.

Isolation of Isosaccharic Acid.—The basic lead acetate precipitate was treated with hydrogen sulfide and the lead sulfide and the undecomposed part of the original lead precipitate were removed by filtration. The precipitate was heated with sulfuric acid on a hot plate for 24 hours, then the supernatant liquid was treated with charcoal and filtered. Crystals separated from the filtrate on standing over night. The crystals were recrystallized from alcohol and then from acetone. They dissolved in water forming an acid solution, which, after neutralizing with ammonia water, gave precipitates with solutions of barium hydroxide, calcium hydroxide and silver nitrate. The crystals gave the color reactions given by hydroxy acids with beta-naphthol and concentrated sulfuric acid. They melted at 185° C. after drying at 100° C. The substance was thus identified as isosaccharic acid. The acid probably did not exist as such in the plant, and very likely was formed by hydrolysis and oxidation of the gum which was present.

Isolation of Gum.—The filtrate obtained after treatment of the basic lead acetate precipitate with hydrogen sulfide was mixed with alcohol. The milky-white precipitate that settled out, was purified by dissolving it in water and reprecipitating two times, and then it was allowed to dry without heat. The substance was completely but slowly soluble in cold water, first swelling and becoming very adhesive; it was readily soluble in hot water, insoluble in alcohol and other organic solvents. An aqueous solution of the substance gave a blue color with iodine solution and gave a positive test with Molisch's reagent, but did not reduce Fehling's solution until after preliminary

boiling with diluted sulfuric acid. Pentoses and galactose were absent. Tests for the presence of sulfate gave negative results. The substance was evidently the gum previously reported in phytolacca. Yield: 13.5 Gm., representing 4.5% of the weight of the drug used.

Separation of a Resin.—The hydroalcoholic filtrate, obtained after precipitation of the gum, was concentrated, the solid matter which deposited was separated, dissolved in alcohol, and the alcoholic solution was evaporated to dryness without heat. A light reddish brown, glistening, brittle, tasteless residue remained. The substance remained brittle when treated with 2% sulfuric acid, it was slightly soluble in ether, soluble in alcohol and in 10% potassium hydroxide solution, from which solution it was precipitated by sulfuric acid. Tests for nitrogen and sulfur gave negative results.

The substance very likely was an acid resin which existed as a complex salt in the root, thus allowing its extraction with water.

The liquid separated from the resin yielded, on further treatment, crystals of oxalic acid, and, on further concentration, crystals of potassium oxalate.

The second decoction was prepared using 4.6 Kg. of fresh poke root. The decoction was treated with basic lead acetate, the precipitate was separated and the excess lead was removed from the filtrate. Part of the filtrate was allowed to evaporate without heat. After two weeks, a dark reddish brown, syrupy mass interspersed with needle-like crystals was obtained. The crystals remained after treatment with alcohol and were identified as potassium nitrate.

The alcoholic solution was allowed to evaporate and the residue was dissolved in water. On addition of sodium hydroxide solution a precipitate formed and was removed by filtration.

Isolation of Saponin.—The precipitate was treated with boiling ether and then with boiling alcohol. The alcoholic solution was evaporated to dryness and the residue was again treated with hot alcohol and the mixture was filtered. The filtrate, on standing, deposited a substance which settled to the bottom of the beaker and adhered to the glass. The deposited substance was white when dried, but on exposure to air its surface appeared to become oily. On shaking with water, a very lasting foam formed. The aqueous solution caused hemolysis of blood and emulsified oil of turpentine. Slight reduction was observed with Fehling's solution, but after boiling with hydrochloric acid a copious precipitate of cuprous oxide was obtained with Fehling's solution.

The substance was thus identified as a saponin.

The solution obtained from the basic precipitate with boiling ether yielded a water-soluble substance (*a*) which gave amorphous precipitates with phosphomolybdic and phosphotungstic acids.

The remainder of the filtrate from the basic lead acetate precipitation was concentrated to a syrup and the residue was extracted with alcohol. The alcohol was allowed to evaporate, the residue was dissolved in water, the solution was made basic with sodium hydroxide and was then extracted with organic solvents. The ethereal solutions yielded several water-soluble fractions which gave amorphous precipitates with phosphomolybdic and phosphotungstic acids.

All the fractions, including (*a*), which gave precipitates with the above-mentioned reagents, were tested by intravenous injection into a male cat with intact vagi under Nembutal anesthesia. No characteristic response was observed immediately in any case with respect to blood pressure or respiration.

SUMMARY AND CONCLUSIONS.

1. The U. S. P. X constants for crude drugs have been determined for poke root.

2. The oil obtained by steam distillation from an alcoholic extract of poke root had a specific gravity of 0.9977, indicating the absence of terpenes (4). The oil was not miscible with 98% alcohol, and may have been composed mainly of lower fatty acids and their esters.

3. Results of chemical and pharmacological tests prove that poke root contains no active alkaloid, and strongly indicate the absence of any alkaloid. However, substances which form amorphous precipitates with some of the so-called

alkaloidal reagents, but which exhibit no basic properties, are present. These substances are undoubtedly responsible for the claims by others that alkaloid is present in the drug.

4. The pharmacological activity of poke root is due to at least two different principles, one or more being soluble in water, the other being soluble in alcohol and insoluble in water. The water-soluble principle or principles appear to be responsible for the strongly irritant properties of the drug, while the alcohol-soluble resin-like principle is responsible for the ascending depressant action on the cerebro-spinal axis of cats.

5. The fixed oil (7) of poke root, extracted by petroleum benzin, proved to be devoid of significant pharmacological activity.

6. Procedures by which the following substances were isolated from aqueous extracts of dried and fresh poke root are given: Hemicellulose, isosaccharic acid (m. p. 185° C.), gum, resin, oxalic acid, potassium oxalate and saponin. The isosaccharic acid probably did not exist as such in the plant, but was formed during the treatment of the lead subacetate precipitate of the gum.

7. Starch was obtained from the expressed juice of fresh poke root. The clear juice did not reduce Fehling's solution, indicating the absence of free reducing sugars.

REFERENCES.

(1) Jenkins, G. L., Jour. A. Ph. A., 18, 573 (1929).
(2) Preston., *Am. J. Pharm.*, 56, 567 (1884).
(3) Thompson, M. R., Jour. A. Ph. A., 24, 24 (1935).
(4) Rosenthaler, L., "Grundzüge der Chemischen Pflanzen Untersuchung," 3rd Edition, 18–22 (1928).
(5) Solis-Cohen and Githens, "Pharmacotherapeutics," 1140 (1928).
(6) *Z. physiol. Chem.*, 16, 391 (1892).
(7) Goldstein, S. W., Jour. A. Ph. A., 25, 636 (1936).

A NOTE ON THE STABILITY OF ERGOT.*

BY L. W. ROWE.

In connection with our recent report on the definite stability of digitalis activity in the crude drug form (1) even when the drug is not stored in air-tight and light-tight containers, it is believed that similar data concerning the stability of *ergot* as crude drug might be of interest. The opinion has prevailed even in scientific circles that these two drugs are relatively unstable and this has resulted in the inclusion in the U. S. P. XI (2) of the following requirement for the storage of ergot: "Preserve Ergot under all conditions of storage and transportation in water-proof and air-tight containers."

Undoubtedly, in the case of ergot at least, the published opinions of Rusby (3, 4, 5) have been partly responsible for the prevalent idea that the drug must be very carefully stored and it is probably true that that drug which has been allowed to mold or has been infested with insects will not be of average potency in addition to being unsuitable from the purely physical standpoint. It has been our experience that it is not necessary to store the drug in air-tight and water-proof containers, but that storage in such a way as to keep the drug reasonably dry is sufficient to

* From the Research Laboratories, Parke, Davis and Company, Detroit, Michigan.

insure its stability. In connection with this question of stability, the following experimental data is of interest.

A sample of Spanish crude drug ergot which had been originally selected for display purposes about 1912, was kept on the laboratory shelf in a 16-oz., glass-stoppered bottle. It was undoubtedly of full standard activity for *Spanish* drug although it bore no identifying number. It had been subject to light but not direct sunlight and to room temperature in addition to some slight interchange of air since the glass stopper was not paraffined and the bottle was opened occasionally. Some ten years ago when the sample of drug was about 15 years old a U. S. P. fluidextract was prepared from a small portion of this sample and its activity determined by the cock's comb bioassay by a procedure similar to that now official in the U. S. P. XI but compared to U. S. P. X standards. The assay showed a potency of at least 80% to 100% of standard.

Six months later a retest of this same experimental fluidextract showed its activity to be fully 80% of standard so the second test served as a check on the earlier one and also that the fluidextract from this drug was reasonably stable in activity.

Now in 1936 when this sample is well over 20 years old (probably nearly 25 years old) two experimental fluidextracts were made from small portions of it and the results of the tests are as follows:

A U. S. P. fluidextract made after defatting the drug in the usual way tested 100% of U. S. P. XI standard by the official method while a fluidextract made without first defatting the drug showed an activity of 120% of U. S. P. XI standard. The apparent *slight increase* in activity during the past ten years is not at all significant since it is within the experimental error of the assay method. These two assays certainly confirm the opinion that the activity of this particular lot of drug has remained remarkably stable over a long period of time (over 20 years) and under conditions of storage that were very ordinary and certainly very different from the rigid conditions of storage required by the U. S. P. XI.

More recently two additional lots of crude drug that are not quite so old were retested with the following results. Both were ground and extracted with the official menstruum without first defatting since it was felt that there is always the possibility of a small amount of activity being removed by the defatting process. Drug No. 276581 which was fully U. S. P. when received fifteen years ago was now found to be nicely 100% in activity. Drug No. 353478 which was also fully U. S. P. when received four years ago was now found to be 110% of U. S. P. XI standard in activity. No. 276581 had been stored for the entire eleven years in a cork-stoppered, clear-glass flask in a laboratory case and so had been subjected to ordinary light and room temperature. No. 353478 had been stored for the four-year period in an ordinary paper sack and so had been subjected to room temperature and humidity changes in the atmosphere during that period.

The moisture content of the samples was determined since the U. S. P. XI sets an upper limit of 8% of moisture on ergot crude drug. The results on four samples are as follows:

25-year old sample	4.25%
No. 276581 (15 yrs. old)	4.41%
No. 353478 (4 yrs. old)	3.91%
Portuguese (4 yrs. old)	4.94%

These results indicated that all four samples are well below the limit set by the U. S. P. for moisture. The only significant fact is that the sample which was really open to the air (kept in a paper sack) was lowest of the four in moisture.

The fact that these three old samples of varying age, stored under ordinary conditions are still equal in activity to the present high U. S. P. XI standard for ergot as crude drug should be strongly indicative of a remarkable stability of potency. These tests should show that the conditions of storage of ergot crude drug as made mandatory in the U. S. P. XI, namely, in water-proof and air-tight containers, are not necessary. They are undoubtedly included because of the known instability of the average extract of ergot and of drug which has been allowed to mold but they place an unnecessary burden upon the importer and the manufacturer who know how to store the drug under proper but ordinary conditions.

It appears that keeping ergot dry is a sufficient protection of activity and that the U. S. P. requirements for storage may well be changed by interim revision to "Preserve ergot under all conditions of storage and transportation in a dry place."

REFERENCES.

(1) Rowe and Pfeifle, JOUR. A. PH. A., 25, 855 (Oct. 1936).
(2) U. S. Pharmacopœia XI Rev., pages 137 and 148.
(3) Rusby, H. H., *New York State Med. Jour.*, 28, 255 (March 1928).
(4) Rusby, H. H., *West Med. Times*, 49, 7–9 (July 1929).
(5) Special Article, *J. A. M. A.*, 95, 722 (Sept. 6, 1930).

THE ASSAY OF THEOPHYLLINE, THEOPHYLLINE MONOETHANOLAMINE AND THEOPHYLLINE WITH ETHYLENE DIAMINE, U. S. P.*

BY ASA N. STEVENS AND DALE T. WILSON.[1]

A few years ago it became necessary for this laboratory to examine the available assay methods for the determination of theophylline. Of the various methods studied two appeared to offer possibilities. These were tried and the following observations were noted.

Kochum (1) described a volumetric method with 0.1*N* $AgNO_3$ using potassium dichromate as an internal indicator. The results obtained by this method varied so widely, due to the inconsistency in the end-point of the titration, that the method was abandoned.

Schmitt (2) used a gravimetric method, recommending silver ammonium chloride as the reagent. The results were found to vary unless the silver chloride precipitation was carried out in a dark room and, further, that a difference of 0.5 mg. in the weight of the silver chloride obtained made a difference of 1.11 per cent in the results.

Finding these methods unsuited to our purpose an attempt was made to develop a more satisfactory procedure. As a result of this investigation the following method is proposed.

---

* Scientific Section, A. PH. A., Dallas meeting, 1936.

[1] Control Laboratories, Eli Lilly and Company.

METHOD.

To 0.2 Gm. of theophylline, accurately weighed, in a 200-cc. flask, add 50 cc. of distilled water and 7 cc. of ammonia water. Warm the mixture on a steam-bath until complete solution is effected. Add 20 cc. of 0.1*N* $AgNO_3$, mix and continue to warm on a steam-bath for 15 minutes. Filter with the aid of vacuum while still warm, washing the precipitate with three 10-cc. portions of distilled water. Cool and acidify the combined filtrate and washings, using nitric acid. Add 2 cc. of ferric ammonium sulfate T.S. and titrate the excess silver nitrate with 0.1*N* KCNS.

Each cc. of 0.1*N* $AgNO_3$ is equivalent to 0.0180 Gm. of anhydrous theophylline.

The results obtained by applying this method to the assay of theophylline are tabulated below. It will be noted that the last sample contained starch as an added diluent. This addition was made in order to determine whether or not theoretical results could be obtained in the presence of a foreign material.

TABLE I.

Sample Wt.	Starch.	Cc. *N*/10 $AgNO_3$ Required.	Anhydrous Theophylline %.	Theoretical %.
0.2 Gm.	....	10.10	90.90	90.90
0.2 Gm.	....	10.10	90.90	90.90
0.2 Gm.	....	10.10	90.90	90.90
0.2 Gm.	....	10.10	90.90	90.90
0.2 Gm.	....	10.10	90.90	90.90
0.2 Gm.	0.2 Gm.	10.10	90.90	90.90

THEOPHYLLINE MONOETHANOLAMINE.

Samples of theophylline monoethanolamine were then assayed for their theophylline content using this method. In this series of assays an excess of monoethanolamine was added to two samples while another sample was mixed with starch. The results appear in Table II.

TABLE II.

Sample Wt.	Starch.	Monoethanolamine.	Cc. *N*/10 $AgNO_3$ Required.	Anhydrous Theophylline %.	Theoretical %.
0.2 Gm.	....	....	8.2	73.80	74.68
0.2 Gm.	....	....	8.2	73.80	74.68
0.2 Gm.	....	Excess	8.2	73.80	74.68
0.2 Gm.	....	Excess	8.3	74.70	74.68
0.2 Gm.	....	....	8.3	74.70	74.68
0.2 Gm.	0.5 Gm.	....	8.4	75.60	74.68
0.2 Gm.	....	....	8.3	74.70	74.68

In order to further check the reliability of the method a number of samples containing theophylline and monoethanolamine were assayed. Each contained a different amount of theophylline. Two of the samples in this series contained talc and two of them starch, as added materials. The results obtained in these assays follow.

TABLE III.

Sample.	Diluent.	Cc. *N*/10 $AgNO_3$ Required.	Theophylline Found Grams.	Theophylline (Theoretical) Grams.	Error %.
A	....	10.30	0.1854	0.1859	−0.26
B	Talc	8.10	0.1458	0.1460	−0.30
C	Talc	10.80	0.1944	0.1925	+0.90
D	Starch	10.70	0.1674	0.1689	−0.69
E	Starch	10.50	0.1890	0.1886	−0.21

THEOPHYLLINE WITH ETHYLENE DIAMINE.

The following data show the comparative results obtained for theophylline and theophylline with ethylene diamine when assayed according to the U. S. P. XI method and by the proposed method herein described.

TABLE IV.—THEOPHYLLINE.

Assay Method.	Wt. of Sample Taken Gm.	Wt. of Anhydrous Theophylline Found Gm.	Cc. $N/10$ $AgNO_3$ Required.	Anhydrous Theophylline %.
U. S. P. XI	2.0	1.8347	...	91.74
U. S. P. XI	2.0	1.7922	...	89.61
Proposed	0.2	..	11.10	99.90
Proposed	0.2	..	11.00	99.00

TABLE V.—THEOPHYLLINE WITH ETHYLENE DIAMINE.

Assay Method.	Sample No.	Wt. of Sample Taken Gm.	Wt. of Anhydrous Theophylline Found Gm.	Cc. $N/10$ $AgNO_3$ Required.	Anhydrous Theophylline %.
U. S. P. XI	A	2.0	1.4077	..	70.39
U. S. P. XI	A	2.0	1.4012	..	70.06
Proposed	A	0.2	..	9.40	84.60
Proposed	A	0.2	..	9.30	83.70
U. S. P. XI	B	2.0	1.3006	..	65.03
U. S. P. XI	B	2.0	1.3175	..	65.88
Proposed	B	0.2	..	8.95	80.55
Proposed	B	0.2	..	8.85	79.65
U. S. P. XI	C	2.0	1.4024	..	70.12
U. S. P. XI	C	2.0	1.4156	..	70.78
Proposed	C	0.2	..	9.00	81.00

COMMENTS.

All the samples of theophylline with ethylene diamine taken for assay were previously dried over sulfuric acid for 48 hours as specified in the U. S. P. XI. The results show that theoretical values are more nearly attained by the method described in this paper than by the method of the U. S. P. XI.

Theoretically the results shown in Table IV should amount to nearly 100 per cent since the assay sample, which had previously been dried over sulfuric acid for 48 hours, was further dried for 17 hours at 100° C. without loss of weight. This test was made in order to prove that the pure theophylline taken for these assays contained no moisture or water of crystallization.

Theophylline with ethylene diamine, according to the U. S. P. XI, should assay not less than 75 per cent and not more than 85 per cent anhydrous theophylline. The assay results in Table V show that the proposed method gives results which are within the official tolerance, while the assay method of the U. S. P. XI gives results that do not meet these standards.

In addition to yielding sub-standard results the U. S. P. XI assay method requires a considerable amount of time. We believe that a shorter, less complicated and more accurate method of assay should be used for the determination of theophylline. The method described in this paper apparently meets these requirements.

CONCLUSION.

1. An accurate method has been developed for the assay of theophylline, which is considerably less involved than the method described in the U. S. P. XI.

2. Its applicability to the assay of Theophylline Monoethanolamine and Theophylline with Ethylene Diamine has been demonstrated.

3. Evidence is presented to show that the method described gives accurate results in the presence of monoethanolamine, ethylene diamine and starch.

The authors wish to express their appreciation to Dr. Edward J. Hughes for his friendly criticisms and advice.

REFERENCES.

(1) Kochum, A., "Volumetric Determination of Theocin (Theophyllin) in Theocin Preparations," *Apoth.-Ztg.*, 23, 230 (1908).

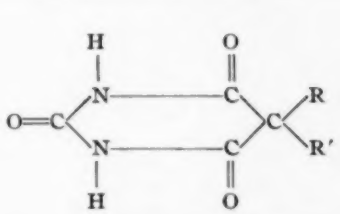
(2) Schmitt, P. W., "A Method for the Quantitative Determination of Theophylline and Ethylene Diamine Theophylline," JOUR. A. PH. A., 19, 821–825 (1930).

2-METHYL-ALLYL SUBSTITUTED BARBITURIC ACID DERIVATIVES.*

BY EDWARD E. SWANSON AND WILLIAM E. FRY.[1]

As previously observed (1), there is a distinct relationship between the pharmacological action and chemical structure of certain barbituric acid derivatives. In the primary or secondary alkyl substituted compounds, with an increasing number of C-atoms in the alkyl substituted group, both the minimal anesthetic dose (M. A. D.) and the minimal lethal dose (M. L. D.) become relatively smaller, but when the alkyl radical is longer than 5 C-atoms, the amount required to produce anesthesia or death in rats again increases. Furthermore, as the alkyl chain lengthens, the ratio between the M. L. D. and M. A. D., or therapeutic index, appears to be gradually greater, and the duration of action becomes shorter. More recently, it has been reported (2) that the substitution of a methyl or an ethyl group on the nitrogen (nitrogen alkyl substituted barbituric acid derivatives) also obviously reduces the duration of action, and this shorter duration of action is independent of the quantity of drug administered.

The present investigation deals with the evaluation of a number of new methallyl (2-methyl-allyl) substituted barbituric acid derivatives synthesized by Doran and Shonle (3), with the general formula:



---

* Scientific Section, A. PH. A., Dallas meeting, 1936.

[1] From the Lilly Research Laboratories, Indianapolis, Indiana.

COMPARISON OF THE PHARMACOLOGIC ACTION OF 22 2-METHYL-ALLYL SUBSTITUTED BARBITURIC ACID DERIVATIVES.

C = Convulsions

Number of Compound.	Barbituric Acids (Methallyls).	Number of Rats.	M. A. D. Mg. per Kg.	M. L. D. Mg. per Kg.	Average Duration of M. A. D. (Min.).	M. L. D. / M. A. D.	Barbituric Acids (Parent Compound).	Number of Rats.	M. A. D. Mg. per Kg.	M. L. D. Mg. per Kg.	Average Duration of M. A. D. (Min.).	M. L. D. / M. A. D.
1	*β-Brom-allyl-methallyl	12	None	500	...	−C	β-Brom-allyl-ethyl	..	...	...	..	..
2	Allyl-methallyl	33	80	180	380	2.25	Allyl-ethyl	..	..	..	..	..
3	Phenyl-methallyl	18	150	200	340	1.33	Phenyl-ethyl	21	150	250	1692	1.66
4	Ethyl-methallyl	33	125	300	360	2.40	Ethyl-ethyl	39	340	480	1400	1.41
5	*n*-Propyl-methallyl	60	120	280	300	2.33	*n*-Propyl-ethyl	49	150	210	1140	1.40
6	1-Methyl-ethyl-methallyl	30	100	220	210	2.20	1-Methyl-ethyl-ethyl	27	170	220	1520	1.37
7	*n*-Butyl-methallyl	90	100	235	110	2.35	*n*-Butyl-ethyl	40	80	200	450	2.44
8	1-Methyl-propyl-methallyl	18	90	200	150	2.22	1-Methyl-propyl-ethyl	35	60	130	600	2.16
9	2-Methyl-propyl-methallyl	67	105	240	115	2.30	2-Methyl-propyl-ethyl	35	120	220	540	1.83
10	*n*-Amyl-methallyl	126	140	330	63	2.35	*n*-Amyl-ethyl	50	70	210	180	3.00
11	1-Methyl-butyl-methallyl	123	60	140	90	2.33	1-Methyl-butyl-ethyl	27	50	110	200	2.20
12	2-Methyl-butyl-methallyl	145	115	290	80	2.52	2-Methyl-butyl-ethyl	48	80	230	190	2.87
13	3-Methyl-butyl-methallyl	106	110	260	87	2.30	3-Methyl-butyl-ethyl	60	80	200	210	2.50
14	1-Ethyl-propyl-methallyl	42	80	160	90	2.00	1-Ethyl-propyl-ethyl	28	65	110	420	1.69
15	*n*-Hexyl-methallyl	36	175	500	60	3.00	*n*-Hexyl-ethyl	95	100	240	80	2.40
16	2-Ethyl-butyl-methallyl	24	150	350	90	2.21	2-Ethyl-butyl-ethyl	..	..	..	..	..
17	Cyclopentyl-methallyl	30	100	250	115	2.50	Cyclopentyl-ethyl	..	..	..	..	..
18	Methallyl-methallyl	36	100	130	105	1.30C	Methallyl-ethyl	33	125	300	360	2.40
19	*n*-Propyl-methallyl-thio	21	200	400	900	2.00C	*n*-Propyl-ethyl-thio	..	..	..	..	..
20	*n*-Butyl-methallyl-thio	18	250	400	600	1.60C	*n*-Butyl-ethyl-thio	..	..	..	..	..
21	1-Methyl-propyl-methallyl-thio	36	None	100	..	−C	1-Methyl-propyl-ethyl-thio	..	..	..	..	..
22	1-Methyl-butyl-methallyl-thio	22	None	100	..	−C	1-Methyl-butyl-ethyl-thio	..	..	..	..	..

* Structure of this compound is doubtful.

wherein R-alkyl radical may be an allyl, β-brom-allyl, phenyl, cyclopentyl, a primary, or secondary alkyl radical with 2 to 6 C-atoms; and R′, a methallyl radical (2-methyl-allyl). Some of these compounds have been prepared by Tabern and Volwiler (4).

Albino rats weighing 77 to 128 Gm. (average, 98 Gm.) were used in this study. Solutions of the sodium salts of the compounds were injected intraperitoneally. The M. A. D., duration of action and the M. L. D. were determined by using 5 animals for each dose level.

As shown in Table I, these barbituric acid derivatives have a distinctly shorter duration. Thus, the substitution of a methallyl (2-methyl-allyl) radical in barbituric acid derivatives, similar to the nitrogen alkyl barbituric acid compounds, produces a change (shorter) in the duration of action. Compounds numbered 19, 20, 21 and 22 (Table I), derivatives of methallyl thiobarbituric acid, cause convulsions with little or no hypnotic or anesthetic properties. There is evidence (5) that certain thiobarbituric acid compounds show pathological changes, and when administered by vein in man (6), thrombosis and soreness of the arm may result.

CONCLUSIONS.

1. A number of methallyl (2-methyl-allyl) barbituric acid derivatives have been synthesized and studied pharmacologically.
2. The substitution of a methallyl radical in barbituric acid derivatives distinctly shortens the duration of action.

REFERENCES.

(1) Swanson, E. E., "Proc. Soc. Exp. Biol. and Med.," 31, 961, 963 (1933–1934).
(2) Swanson, E. E., JOUR. A. PH. A., 25, 858 (1936).
(3) Doran, W. J., and Shonle, H. A., *J. Am. Chem. Soc.* (in press).
(4) Tabern, E. H., and Volwiler, D. L., *Ibid.*, 57, 1961 (1935).
(5) Gruhzit, O. M., Pathological Section Joint Session of the Federation of American Societies for Experimental Biology, Washington Meeting, March 25–28, 1936.
(6) Lundy, J. S., *Ill. M. J.*, 70, 134 (1936).

DRUG EXTRACTION. XIII. THE EXTRACTION OF IPOMEA.*,[1]

BY WILLIAM J. HUSA[2] AND PAUL FEHDER.

The U. S. P. X specified alcohol as the menstruum for the preparation of resin of ipomea. The N. F. VI changed the menstruum to a mixture of 9 volumes of alcohol and 1 volume of water. In the present paper a report is made of experiments which were carried out to determine the relative value of the U. S. P. X and N. F. VI menstrua from the standpoint of rate of extraction, purity and yield of resin.

EXPERIMENTAL DATA.

Effect of Variation in Solvents on Rate of Extraction.—Percolation experiments were conducted using ipomea, in moderately coarse powder, containing 21.1 per cent of resin by the N. F.

---

* Scientific Section, A. PH. A., Dallas meeting, 1936.

[1] This paper is based on part of a dissertation presented to the Graduate Council of the University of Florida by Paul Fehder, in partial fulfilment of the requirements for the degree of Doctor of Philosophy. [2] Head Professor of Pharmacy, University of Florida.

VI assay. Two 500-Gm. portions of ipomea were extracted with alcohol, using 300 cc. of moistening liquid and with a maceration period of 48 hours after packing. Two other percolations were carried out in the same manner with the exception that the menstruum was a mixture of alcohol 9 volumes—water 1 volume. Percolation was conducted at the rate of about 0.5 cc. per minute, the percolates being collected in successive fractions of 250 cc., 250 cc., 500 cc. and 500 cc. The various fractions of percolate were assayed for resin by the N. F. VI assay and for total extractive. The results are shown in Table I, the figures reported being the averages of duplicate experiments.

TABLE I.—PERCOLATION OF IPOMEA WITH DIFFERENT MENSTRUA.

	Gm. of Resin in Various Fractions of Percolate.		Gm. of Total Extractive in Various Fractions of Percolate.	
Percolates.	Alcohol.	Alc. 9 Vol.—Water 1 Vol.	Alcohol.	Alc. 9 Vol.—Water 1 Vol.
250 cc.	60.5	63.7	65.3	70.3
250 cc.	33.1	32.9	35.6	38.1
500 cc.	7.8	6.9	10.3	14.3
500 cc.	1.1	1.5	2.6	6.3
Total	102.5	105.0	113.8	129.0

The results in Table I indicate that the rate of extraction of resin from ipomea is practically the same with alcohol as with a mixture of 9 volumes of alcohol and 1 volume of water. From 500 Gm. of drug, the more aqueous menstruum removed 2.5 Gm. more resin and 15.2 Gm. more total extractive.

Comparison of U. S. P. X and N. F. VI Methods of Preparing Resin of Ipomea.—Experiments were carried out to determine whether or not the change in official menstruum has any effect on the purity or yield of resin of ipomea. Two different lots of resin of ipomea were prepared from 500-Gm. portions of ipomea in moderately coarse powder, using alcohol as the menstruum; each 500-Gm. portion of drug was moistened with 300 cc. of menstruum before packing and there was a maceration period of 48 hours after packing. Percolation was carried out at an average rate of about 0.6 cc. per minute, 1500 cc. of percolate being collected from each 500-Gm. portion of drug. Each 1500-cc. portion of percolate was evaporated on a water-bath to a thin syrup, which was poured in a thin stream, with constant stirring, into 700 cc. of hot distilled water. The precipitated resin was allowed to settle, the supernatant liquid was decanted and the precipitate washed twice, by decantation, with 700-cc. portions of hot distilled water. Each lot of resin was dried to constant weight in a vacuum oven at 75–80° C.

Two portions of resin of ipomea were also prepared from 500-Gm. portions of ipomea, keeping all experimental details the same as before except that the N. F. VI menstruum of alcohol 9 volumes—water 1 volume was used.

The average yield of resin of ipomea obtained from the two 500-Gm. portions of ipomea by the U. S. P. X method was 19.5%, while by the N. F. VI method the yield was 20.3%.

The various lots of resin were assayed by the N. F. VI assay method which is specified for determining the percentage of resin in ipomea. Taking the average of several determinations, the resin prepared by the U. S. P. X method was found to assay 98.2% resin while the resin prepared by the N. F. VI method assayed 96.7%.

DISCUSSION OF RESULTS.

It was found that the rate of extraction of resin of ipomea is practically the same with the U. S. P. X menstruum (alcohol) as with the N. F. VI menstruum (alcohol 9 volumes—water 1 volume). The N. F. VI menstruum gives a slightly higher yield of resin, but the product is not as pure as that obtained by the U. S. P. X method. On the basis of the purity of the product, it is concluded that the U. S. P. X menstruum is preferable to the N. F. VI menstruum.

The results of the present study are in accord with the results obtained by Husa and Fehder (1) in a similar investigation of the preparation of resin of jalap in which it was found that the more aqueous menstruum had the disadvantage of

causing a great increase in total extracted matter, thus increasing the bulk of syrupy extract to be handled and greatly increasing the proportion of impurities to be removed during the precipitation and washing of the resin.

SUMMARY.

The N. F. VI menstruum for Resin of Ipomea (alcohol 9 volumes—water 1 volume) gives a slightly higher yield than that obtained with the U. S. P. X menstruum (alcohol). However, the N. F. VI product is less pure than that obtained by the U. S. P. X method. On the basis of the purity of the product, it is concluded that the U. S. P. X menstruum is preferable to the N. F. VI menstruum.

REFERENCE.

(1) Husa, W. J., and Fehder, P., JOUR. A. PH. A., 26, 121 (1937).

METHODS USED IN THE DETERMINATION OF THE ALKALINITY IMPARTED TO WATER BY AMPUL GLASS.

BY R. K. SNYDER AND E. N. GATHERCOAL.*,[1]

INTRODUCTION.

Chemists, perhaps, first used hermetically sealed glass containers for the preservation of materials sensitive to air and moisture.

Needham, 1759, and Spallanzani, 1769, mention the preservation of sterile putrescible liquids in flasks hermetically sealed by drawing out the necks of the flasks.

Limousin, inventor of the cachet, was the first to propose (1886) the method of dispensing sterile fluids in ampuls. French pharmacists were the first to offer injectable medicaments in such containers. Little change has been made during the subsequent years in the shape and appearance of ampuls.

The fact was noted rather early in the use of ampuls that certain solutions, notably the alkaloidal solutions, were visibly affected by the alkalinity produced by the glass during the sterilization and aging of the ampul solution.

AMPUL GLASSES.

The glass first used in ampuls was of the usual soda-lime type containing about 70% of SiO_2, 14% of Na_2O and 13% of CaO. Rather early in the present century glass was produced containing boric oxide. This Jena glass was found to be much more resistant to corrosion by reagents than was the ordinary soda-lime glass. Jena glass contained about 4% of B_2O_3, but in 1911 a new Jena glass was produced containing about 65% of SiO_2, 11% of B_2O_3, 4% of Al_2O_3, 11% of ZnO and 7.5% of Na_2O. Jena glass is harder to fuse than soda-lime glass and yet it can very nicely be used for ampuls, and has been widely introduced for this purpose.

A few years later, Pyrex glass was introduced for laboratory use. This glass contains about 80% of SiO_2, 12% of B_2O_3, 2% of Al_2O_3 and 4% of Na_2O. This glass is difficult to fuse, due to its low alkalinity and high content of silica. It is of high resistance to corrosion due to

---

* Scientific Section, A. PH. A., Dallas meeting, 1936.

[1] We wish to express our appreciation for advice and suggestions, as well as for the contributions of material which has aided this work, to: F. E. Bibbins, Eli Lilly & Co.; E. B. Carter, Abbott Laboratories; J. B. Fullerton, Upjohn Co.; C. C. Neal, Sharp & Dohme; F. O. Taylor, Parke, Davis & Co.

the high acidic oxide content (SiO_2 and B_2O_3 constitute more than 90% of the glass) and the low basic oxide content. Because of its high fusing point, requiring the oxy-acetylene torch, it is not practicable for ampuls.

In very recent years the Kimble Co. of New Jersey has introduced Non-Sol glass and Non-corrosive glass. Non-Sol glass contains about 67% of SiO_2, 6% of B_2O_3, 2.5% of Al_2O_3, 8% of ZnO, 3.4% of MgO and 11% of Na_2O. The Kimble N. C. glass contains about 73.8% of SiO_2, 9.6% of B_2O_3, 5.5% of Al_2O_3, 3.0% of BaO, 0.6% of ZnO, 0.5% of MgO, 0.6% of CaO, 6.5% of Na_2O, 0.1% of As_2O_3. Its alkalinity and fusibility compare very favorably with the best Jena glass and it is now used extensively in America for ampuls.

THE ATTACK OF WATER ON GLASS.

It is incorrect to speak of the solubility of a glass as we would discuss the solubility of a salt. The action is one of diffusion and disintegration and not one of true solution. The mechanism of the attack of water upon an ordinary glass is not well known, but is highly selective. Sodium silicate is leached from the glass and this undergoes hydrolysis so that the solution contains essentially sodium hydroxide and colloidal silicic acid. Since calcium compounds and other earths are virtually insoluble in such a solution, we find in the filtered solution obtained by digesting powdered glass with water very little except soda and silica. Because of the insolubility of the lime or lime silicate and the relative insolubility of silica, these materials exert a protective action which causes the attack to proceed much more slowly as time goes on. It can be shown that the quantity of soda removed from the glass is approximately proportional to the square root of the time of exposure to the water.

The durability of a glass, or its fitness for use in various applications, is measured by estimating one special property—the quantity of alkali yielded to water under definite conditions.

THE ALKALINITY TESTS.

The Phenolphthalein Test, in which a dilute aqueous solution of the indicator is heated in the ampul, was the first test used to determine the alkalinity imparted to water by ampul glass. If the solution in the ampul becomes pink, the ampul is considered unfit for use. This test, standarized as to concentration of solution, length of heating period, and temperature was adopted in N. F. V (1926) when ampuls became official. The same test has been carried over into N. F. VI.

The N. F. VI Subcommittee on Ampuls recognized that the phenolphthalein test of the N. F. V was not sufficiently restrictive as regards ampul glass. Some attention was given to other tests for alkalinity in glass, but in the vast detail of preparing 28 new ampul monographs, an intensive study of these tests was postponed until this year.

The details of various methods employed for determining the alkalinity imparted to water by ampul glass are presented as follows:

N. F. VI Method.—Glass used for ampuls must be of high quality, particularly in regard to its resistance to water and heat. After cleansing, it shall pass the following test for solubility and reaction as a minimum requirement of quality: Mix 1 volume of a 1 per cent solution of phenolphthalein in neutral alcohol with 99 volumes of distilled water, and fill the ampuls to be tested; seal them, and immerse them in live steam or in boiling water for six hours; after cooling, the contents of the ampuls show no pink color, and no loose scales or flakes of glass.

NOTE: The spelling of "Ampul" is in accord with the Pharmacopœia quoted; British "Ampoule," U. S. P. "Ampul."

British Pharmacopœia Method (*Whole Ampuls*).—Not less than six ampoules are used, and each ampoule must comply with the test. The ampoules used must be from 0.5 cc. to 25 cc. in capacity.

Fill the ampoules to their prescribed capacity with acid solution of methyl red, seal by means of a blow-pipe, and heat in steam at a pressure of 15 lbs. per square inch for half an hour. Cool and examine the color of the solution. If necessary, when the ampoules are of colored glass, the solution is removed for examination on to a thoroughly washed white glazed tile. The glass passes the test if the color of the test solution has not changed from pink to the full yellow of methyl red, as indicated by comparing it with that of a solution prepared by adding 0.1 ml. of $N/10$ sodium hydroxide to 10 ml. of the acid solution of methyl red.

NOTE: Ampoules which have once passed the test on whole ampoules, may fail to do so after being stored. Whenever possible the test is carried out not more than fourteen days before the ampoules are to be used. If a batch of ampoules, which has passed the test but has been stored, does not subsequently pass the test, a sample of them may be resubmitted to the test after each ampoule has been washed internally with a 5 per cent v/v aqueous solution of glacial acetic acid followed by three washings with water. If the sample then passes the test each ampoule of the batch is similarly washed before being used.

British Pharmacopœia Method (*Crushed Glass*).—(*a*) Testing the apparatus to be used. A test solution consisting of 100 ml. of water, 0.4 ml. $N/100$ hydrochloric acid and 0.4 ml. of strong solution of methyl red is boiled, and, while boiling, transferred to a conical flask of resistant glass of 250 ml. capacity. The flask is fitted with a reflux condenser, or with a suitable condensing apparatus, made of resistant glass. The flask is quickly placed in a bath of boiling water, so that the contained solution is below the level of the water in the bath. Boiling is continued for one hour. At the end of this time the color of the solution is observed. If any change of color has taken place, the flask and the condenser are unsuitable for use in the test.

(*b*) Test of the glass. The glass is crushed and sieved, the particles which pass through a No. 25 sieve but fail to pass through a No. 36 sieve being used for the test. Five grams of the sieved glass are washed free from dust in a small conical flask by repeatedly washing with alcohol (95 per cent), and are dried at 100° C. The sieved glass is placed with 100 ml. of a fresh portion of the test solution into the conical flask, and the test is repeated, but the boiling is continued for half an hour instead of an hour. The glass passes the test, if at the end of this time the color of the test solution has not changed from pink to the full yellow color of methyl red, as indicated by comparing it with that of a solution prepared by adding 0.1 ml. of $N/10$ sodium hydroxide to 10 ml. of the test solution.

Strong Solution of Methyl Red: Dissolve 0.04 gram of methyl red in 50 ml. of alcohol (95 per cent), add 1.5 ml. of $N/20$ sodium hydroxide, or a quantity sufficient to ensure that the color of the solution corresponds to about p_H 5.2 and dilute to 100 ml. with water.

Acid Solution of Methyl Red: Mix 20 ml. of strong solution of methyl red with 8.3 ml. of $N/50$ hydrochloric acid and a sufficient quantity of water to produce 1000 ml.

Comments: We sifted the glass through No. 20 and No. 40 sieves as No. 25 and No. 36 sieves were not available. This may have made some difference in the results we obtained, for the alkalinity yielded by crushed glass increases according to its fineness of particles.

German Pharmacopœia Method.—Five grams of coarsely crushed glass is placed in a Jena glass flask, previously rinsed with hot distilled water, with 100 cc. of water to which has been added 0.3 cc. of $N/100$ hydrochloric acid and 1 drop of methyl red solution. The flask is then heated for one-half hour in a boiling water-bath. At the end of the heating period the color of the solution is observed. The glass passes the test if the color of the solution has not become completely yellow.

Comment: This method is listed here, though we did not work with it. The method states no degree of fineness to which the glass shall be reduced and this is an omission of a most important detail. (See comment above.) Furthermore, the test is very similar to that of the British Pharmacopœia for crushed glass as given above.

Titration Method, Lilly.—Break sample in a perfectly clean mortar and grind to a 40 to 60 powder. First put through a 40-sieve, discarding all coarse material. The portion passing the 40-sieve is next put in a 60-sieve. All that passes this sieve is also discarded. All that will pass the 40-sieve and will not pass the 60-sieve is suitable for use.

Ten-gram sample is weighed into a 250-cc. clean Pyrex (or other insoluble glass) flask, 20 cc. $N/20$ hydrochloric acid added and the mixture allowed to stand 24 hours. It is then titrated with $N/10$ sodium hydroxide using phenolphthalein indicator. Alkalinity calculated as per cent potassium hydroxide.

Comments: This method was presented to us by Eli Lilly & Co. The following modification of the method was also tried out: To the powdered glass in the flask add 25 cc. of $N/50$ hydrochloric acid; back titrate with $N/50$ sodium hydroxide using phenol red indicator; report as the number of cc. of $N/50$ hydrochloric acid consumed.

Titration Method, Kimble.—If necessary the sample glass is washed with distilled water and then dried. Break up the glass in a steel mortar and screen out using U. S. Standard sc. eens No. 40 and No. 60. Spread out the No. 40–60 grains on a clean sheet of white paper and remove any iron derived from the mortar by repeated use of a magnet.

Place a 10-Gm. sample in a 125-cc. Pyrex (or other insoluble glass) flask, add 40 cc. of freshly boiled distilled water and cap the flask loosely with a small beaker or tin foil. A blank should be prepared in the same manner excluding the crushed glass. Place the flasks in an autoclave and heat for 30 minutes at a pressure of 15 pounds. After the heating, remove the flasks from the autoclave, cool rapidly in cold water and when cool titrate with $N/50$ hydrochloric acid, using phenol red indicator. Report number of cc. of $N/50$ hydrochloric acid used.

Hydrogen-Ion Concentration Method Using the Quinhydrone Electrode.—Clean ampuls are filled with freshly boiled distilled water, of which the p_H has been determined with a potentiometer using a quinhydrone electrode. The ampuls are then sealed, and autoclaved for 30 minutes at 15 pounds pressure. When cooled to 25° C. the ampuls are opened and the p_H of the solute from the ampul is determined with the same apparatus. The difference between the two values is due to the alkalinity yielded by the ampul.

Hydrogen-Ion Concentration, Colorimetric Method.—Clean ampuls are filled with freshly boiled distilled water of which the p_H has been determined colorimetrically according to the directions for colorimetric p_H determinations in the U. S. P. XI. They are then sealed and autoclaved for 30 minutes at 15 pounds pressure. When cool, the ampuls are opened and the p_H of the solution contained in them is determined by the same method. The amount of difference in p_H, between the water placed in the ampuls and the solution removed from them determines the amount of free alkalinity of the glass.

Bromthymol Blue Method.—The U. S. P. XI colorimetric Solution of Bromthymol Blue was diluted with freshly boiled distilled water to make a concentration of 8 mg. of dye per liter. Although this concentration is less than that of phenolphthalein in the N. F. VI solution, it is the same as that of methyl red in the B. P. test and falls within the limits of the U. S. P. XI for the dilution of the indicator in colorimetric p_H determinations.

Clean ampuls are filled with this solution and sealed. One is kept for comparison and the rest are autoclaved for 30 minutes at 15 pounds pressure. When cool, the color is observed and compared with that of the unheated ampul.

RESULTS OF OUR TESTS.

A sufficient number of empty glass ampuls were prepared in the laboratory or were supplied by certain manufacturers so that 13 different kinds were available, and representing the several kinds of glass that have been used for ampuls.

Several methods of colorimetric testing (though but four methods are reported here); three titration methods and two hydrogen-ion concentration methods were conducted on the 13 lots of ampuls so far as the supply of each was sufficient. The work is being continued with these and other methods of estimating alkalinity. Also tests to determine the conductivity of water after being heated in ampuls are under way.

Some of the results are presented in Tables I and II.

DISCUSSION OF THE METHODS USED.

Cleansing the Ampuls before Testing.—In several of the methods described, the ampul (or glass) is to be cleansed before the test is conducted.

The N. F. method directs any suitable method of cleansing but sugggests the use of distilled water containing 0.1% of hydrochloric acid, boiling for five minutes and thoroughly rinsing once with distilled water. The B. P. method suggests the cleansing of ampuls that do not pass the test, by washing with 5% aqueous solution of acetic acid, followed by three washings with water. The B. P. method for crushed glass requires that the properly sifted glass be washed with alcohol to remove dust. The Kimble titration method suggests the washing of the glass with distilled water before it is crushed.

Our work indicates that there usually is an alkaline film on the surface of ampul glass. It has been noted repeatedly that ampuls have responded to the bromthymol blue test when they were filled with the reagent before being rinsed and before the application of heat. When this film had been rinsed off, only ampuls of alkaline glass responded to the test when heated.

The effect of high temperatures, such as are used when ampuls are drawn from tubing or are sealed, is but slight either upon the film or the alkalinity of the glass itself. This effect, if any, would decrease alkalinity rather than increase it, for alkali is somewhat volatile at these high temperatures.

The use of acid for cleansing is not necessary according to our work. Strong acid, particularly, is to be avoided as it not only removes the film but some of the alkalinity of the glass itself; thus an ampul so treated would appear, according to the test, to be of less alkaline glass than it really is.

Dilute acids apparently are no more efficient than water, as the film is water soluble. When acids are used careful washing is required to insure their complete removal and much additional time is consumed, especially so when the dilute acid is heated in the ampul.

Three rinsings with distilled water followed by a rinsing with the reagent solution to be used is fully adequate to cleanse the ampul for the test.

TABLE I. SHOWING RESULTS OF COLOR TESTS.

Glass.	N. F. VI.	B. P. for Ampuls.	B. P. for Crushed Ampuls.	Bromthymol Blue.
No. 1	−	+	+	Blue
No. 2	−	+	+	Blue
No. 3	+	+	+	Blue
No. 4	−	+		Green
No. 5				
No. 6	−	+	+	Green
No. 7	−	−		−
No. 8	−	−		Blue
No. 9	−	−	−	−
No. 10	−	−		−
No. 11	−	−		
No. 12	−	−	−	−
No. 13	−	−		

TABLE II. SHOWING RESULTS OF TITRATION TESTS.

Kimble Method.	Lilly Method.	Lilly Method Modified.	p_H Colorimetrically.	p_H by Quinhydrone Electrode.
6.80 cc.	0.0224%	2.30 cc.	Above 8	6.50
5.60 cc.	0.0196%	2.15 cc.	Above 8	6.95
8.00 cc.	0.0252%		Above 8	7.20
8.20 cc.				6.25
5.80 cc.	0.0224%	2.00 cc.		
2.00 cc.	0.0112%			5.90
0.30 cc.				
0.30 cc.				6.40
0.30 cc.	0.0056%	0.15 cc.	6.6	5.80
	0.0112%			
0.50 cc.				
0.40 cc.			6.6	5.80

− No change, glass passed the test. p_H of water colorimetrically 6.4.

+ Change in color, glass failed the test. p_H of water by quinhydrone electrode 5.4.

Glass.	
No. 1	Ampuls made from bacteriological culture tubes.
No. 2	Ampuls made from ordinary soft glass test-tubes.
No. 3	Ampuls made from Kimble flint glass tubing.
No. 4	Ampuls for powders.
No. 5	Syringe barrels.
No. 6	Non-sol ampuls, 50 cc.
No. 7	Kimble ampuls, 2 cc.
No. 8	Kimble ampuls, 5 cc.
No. 9	Kimble ampuls, retempered, 10 cc.
No. 10	Jena ampuls for powders, small size.
No. 11	Jena ampuls, 5 cc.
No. 12	Jena ampuls, 25 cc.
No. 13	Violax ampuls, 5 cc.

Heating the Water or Test Solution in the Ampul.—In the N. F. method the sealed ampuls containing the test solution are to be heated in live steam or in boiling water for six hours. In the B. P. method they are to be heated in the autoclave for 30 minutes at 15 pounds pressure.

Our work indicates that the boiling method has very little, if any, advantage over the autoclaving method. Autoclaving has a great advantage in the saving of time. After our first experimental work demonstrated this point—we have used autoclaving exclusively (except in the N. F. method).

The N. F. VI Method.—This method is entirely unsatisfactory. Any glass except the poorer grades of soda-lime glass will pass the test. Furthermore, the test requires much more time than nearly any of the other methods of testing.

Phenolphthalein begins to change color at a p_H of 8. Any ampul glass that will increase the alkalinity of freshly distilled water (with a p_H of about 6.5) to a p_H of 8, is not suitable for containing injectable solutions. Furthermore, the alkaline form of phenolphthalein is not stable; in alkaline medium it changes to a colorless trivalent ion derived from the carbinol form. Therefore, alkaline solutions of phenolphthalein fade on long standing and more rapidly if heat is applied. For instance, when we filled two soft-glass ampuls of one lot, one with the N. F. test solution of phenolphthalein and the other with distilled water and autoclaved them; the one with the test solution remained colorless; the other, opened and receiving 1 or 2 drops of phenolphthalein T. S., immediately became red.

The B. P. Method for Whole Ampuls.—This method gives fairly satisfactory results. The reagent used is an $N/7500$ solution of hydrochloric acid containing methyl red as an indicator. When the acid has been neutralized the indicator changes to a yellow color. The test passes all ampuls that do not develop a full yellow color. The soda-lime glasses will not pass the test but several of the glasses tested gave only an orange color, therefore passing the test. All of the better grades of ampuls failed to change the color at all.

From the results obtained in our work, the test would be more suitable if no change from the acidic red (or pink) of the indicator were permitted.

The volume of the test solution in the ampul in relation to the area of glass exposed to the solution plays an important rôle in the test. Hence the size of ampuls to be tested is limited to a maximum of 25 cc. This is an undesirable limitation.

B. P. Method for Crushed Glass.—This method, while giving satisfactory results and being more selective than the above method, is undesirable on a technical basis. The test solution is so sensitive that there is the possibility of other factors besides the alkalinity of the glass affecting the final results.

Bromthymol Blue Method.—This procedure is the N. F. VI method with bromthymol blue substituted for phenolphthalein and autoclaving in place of boiling. This test gives quite satisfactory results because the p_H range of the indicator is more suitable (6.0 to 7.6) but the change in color to a green or a blue can be read as indicating roughly the degree of alkalinity. The indicator does not seem to be affected by the heating.

Hydrogen-Ion Concentration Method Using the Quinhydrone Electrode.—The results obtained with this method in our work have not been satisfactory. They are variable, cannot be duplicated and do not correspond to those obtained by the colorimetric method. This variability of results as obtained on water by the quinhydrone electrode has been observed by other workers.

Hydrogen-Ion Concentration by the Colorimetric Method.—This method has given entirely satisfactory results. By determining the p_H of the freshly distilled water just before using it in the ampul, and then of the solution after heating in the ampul and cooling, the difference in p_H between the two becomes a fairly constant figure for that lot of ampuls and can be readily duplicated. It is suggested tentatively that the maximum change be limited to 0.5 p_H.

Titration Method, Kimble.—This procedure has given very satisfactory results. It permits a very close differentiation in the alkalinity of ampul glass. It also permits the testing of used ampuls more easily than the other methods do, except the titration method, Lilly. Furthermore glassware may be tested in which ampul solutions are prepared or stored. A disadvantage of this method is the time consumed in grinding and sifting the glass, which requires about 45 minutes for a 10-Gm. sample. Another disadvantage is the relatively large number of ampuls required to obtain a sample. It was found that it was hardly possible to get more than one-third of the glass that would pass through a No. 40-screen but not pass through a No. 60-screen. This means at least 60 Gm. of the glass was required to produce two 10-Gm. samples. Two types of mortars were tried for efficiency, the ordinary cast-iron mortar and the Plattner hardened steel mortar. They both require about the same amount of time to prepare a 10-Gm. sample, but the former produced about 35% of particles of the desired size while the latter produced about 25%. However, the latter was much easier and more pleasant to use.

It is suggested tentatively that a titration value of 0.5 cc. be set as a limit for the alkalinity of a 10-Gm. sample.

Titration Method, Lilly.—Both the original method of Lilly and the modification of it have given very satisfactory results; however, the latter is to be preferred because the difference in values between different kinds of glass is more apparent. The advantages and disadvantages of this method are the same as those of the titration method, Kimble, except that it takes longer, due to the 24-hour standing period.

Used Ampuls.—Tests were run on ampuls of commercial makes and on ampuls made of both hard and soft glass which were filled in this laboratory and then aged. The results of these tests are listed in the following table and indicate that the storage of solutions in the ampuls does not interfere with the test providing the used ampuls have been properly cleansed.

The tests used were the B. P. for whole ampuls and the titration method, Kimble. Both gave good results. However, unless the ampuls are of such size that they can be handled easily in the flame for redrawing and sealing, the titration method is more convenient besides being more desirable for the reasons listed in the comments on the method.

TABLE III.—SHOWING RESULTS OF TESTS ON USED AMPULS.

		Kimble Method.	B. P. Method.
1	Culture tube glass	6.80 cc.*	Orange
1*a*	Culture tube ampuls that have been filled with boiled redistilled water, sterilized for 30 minutes at 15 pounds, aged 22 days, emptied and dried	7.30 cc.*	Changed from red to a slightly pinkish yellow, almost a complete yellow
1*b*	Culture tube ampuls filled with ampul solution of Green Iron and Amm. Cit., sterilized for 30 minutes at 65° C. on three successive days, aged 22 days, emptied and washed	7.00 cc.*	Same results as in No. 1*a*
2	Lilly's retempered ampuls	0.30 cc.	No change
2*a*	Lilly's retempered ampuls treated as in No. 1*a*	0.20 cc.	No change
2*b*	Lilly's retempered ampuls treated as in No. 1*b*	0.20 cc.	No change
3	Ampuls of Sodium Iodide, Lilly and Abbott, emptied, cleansed and dried	0.25 cc.	.....

3*a*	Ampuls of Sodium Cacodylate, S. & D. and P. D. Co., emptied, cleansed and dried	0.35 cc.	.....
3*b*	Ampuls of Green Iron and Ammonium Cit., S. & D., emptied, cleansed and dried	0.25 cc.	.....

Kimble Method: Kimble titration method on powdered glass.
B. P. Method: B. P. Methyl red test on whole ampuls.
* 5-Gm. sample was used, but the report is based on 10 Gm. of the powdered glass.

SUMMARY.

1. For the cleansing of ampuls preparatory to testing them for the free alkalinity of the glass, it has been found that several rinsings with distilled water is all that is necessary.

2. Autoclaving the ampuls filled with water or the test solution for 30 minutes at 15 pounds pressure is to be preferred to boiling for six hours.

3. The phenolphthalein test for free alkalinity in ampul glass as found in the National Formulary VI is entirely unsatisfactory and should be replaced by a better method of testing.

4. The Hydrogen-Ion Concentration Colorimetric Method, in which is determined the amount of difference in p_H between that of the freshly boiled distilled water to be used in the ampul and that of the solution removed from the ampul, is quite satisfactory. This difference can be readily duplicated and is fairly constant for the individual ampuls of a lot of ampuls.

It is recommended that a difference of 0.5 p_H be the maximum limit of change.

5. The Kimble Titration Method is satisfactory. It indicates the amount of free alkalinity in glass very closely. The marked disadvantage of the method is that it requires such a large amount of crushed glass, approximately 60 Gm., to run the test in duplicate.

It is recommended that a titration value of 0.5 cc. of $N/50$ hydrochloric acid be set as a limit for the alkalinity of a 10-Gm. sample.

REFERENCES.

"National Formulary VI" (1936).
"United States Pharmacopœia XI" (1936).
British Pharmacopœia (1932).
German Pharmacopœia (1926).
Acree and Fawcett, *Ind. & Eng. Chem., Anal. Ed.*, 78 (1930).
Baillie and Wilson, *J. Soc. Chem. Ind.*, 41, 45T (1922).
Dawson, *J. Phys. Chem.*, 29, 554 (1925).
Eleizegui, *Chimie & industrie*, 24, 372 (1930).
Êwe, *Am. J. Pharm.*, 92, 582 (1920).
Fales and Nelson, *J. A. C. S.*, 37, 2781 (1915).
Gabel, JOUR. A. PH. A., 23, 1174 (1934).
Kolthoff, "The Colorimetric and Potentiometric Determination of p_H," Wiley (1931).
Limonsin, *Bull. Gen. de Therap.*, 316 (Apr. 15, 1886).
Matthews, JOUR. A. PH. A., 20, 767 (1931).
Pegurier, *Chemist & Druggist*, 74, 169 (1909).
Pritchard, *Pharm. J.*, 124, 539 (1930).
Scholes, *Modern Glass Practice*, Industrial Publications, Inc. (1935).
Williams, *J. A. M. A.*, 78, 1025 (1922).

THE COLOR OF MORPHINE SULFATE.*

BY J. M. ORT AND W. G. CHRISTIANSEN.[1]

Inspection of several market brands of morphine sulfate has revealed that these products appear to be of somewhat different shades of whiteness as judged by the unaided eye. Solutions of some of these different products also appear to be distinctly grayer than solutions of some of the others. These differences, for both solids and solutions, are usually not large and probably would be overlooked entirely by the casual observer. When, however, the cubes of the several brands are observed carefully side by side, or large volumes of their solutions are compared simultaneously, these differences become definitely discernible.

Such differences in color, both among the solid samples of the drug and among their aqueous solutions, show that these products are not all of uniform quality.

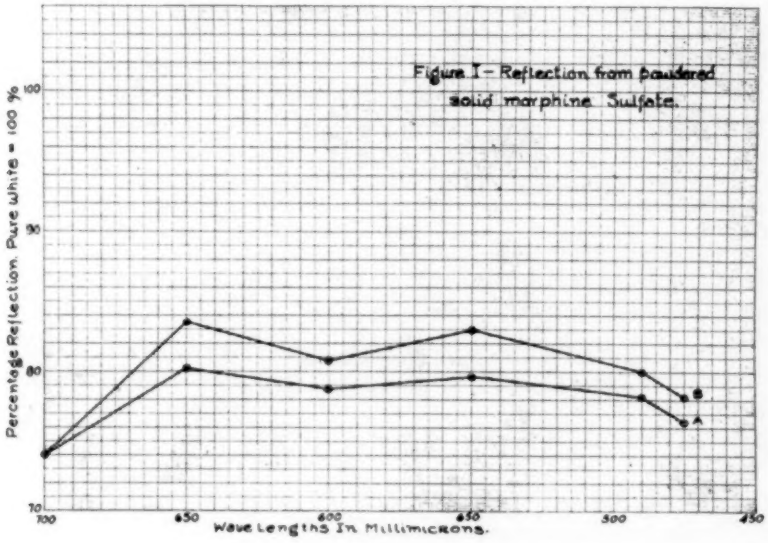


Fig. 1.

The first impulse is, of course, to assume that the cubes which look the whitest are the purest morphine sulfate. However, it was considered advisable to investigate this point since the unaided eye can be deceived as to the comparative qualities (both color and intensity) of different beams of light which reach it after being reflected or transmitted by any material which absorbs some of the light incident upon it. (Fig. 1.)

In order to determine the real nature of the light which is reflected by the various samples of morphine sulfate studied, or transmitted by their solutions, spectrometric analyses of such light were made. Figure 1, for example, gives curves showing the per cent reflection from two of the market brands of morphine sulfate studied, designated A and B, and Fig. 2 shows the transmission curves for solutions of the same products.

* Section on Practical Pharmacy and Dispensing, A. PH. A., Dallas meeting, 1936.

[1] Research Department of the Chemical and Pharmaceutical Laboratories, E. R. Squibb and Sons, Brooklyn, N. Y.

It can be seen that the solid morphine sulfate of brand B reflects a little more light throughout the visual spectrum than does brand A morphine sulfate. A pure white solid would, of course, reflect 100% of the light of all wave-lengths incident upon it. This part of the color analysis simply confirms ordinary visual observation. Since about 80% of the light was reflected by both these samples throughout the range of color in which the human eye is most sensitive, it is obvious that both samples should appear as approximately white or grayish white solids. However, when closely examined side by side, brand B appeared the whitest.

When, now, the transmission curves of Fig. 2 are examined, an apparent inconsistency is noticed. Solutions of brand A transmit the most light throughout the visual spectrum; a perfectly transparent material would, of course, transmit 100% of the light of all wave-lengths passing into it. This can only mean that solutions of brand B contain certain impurities which absorb light and which are

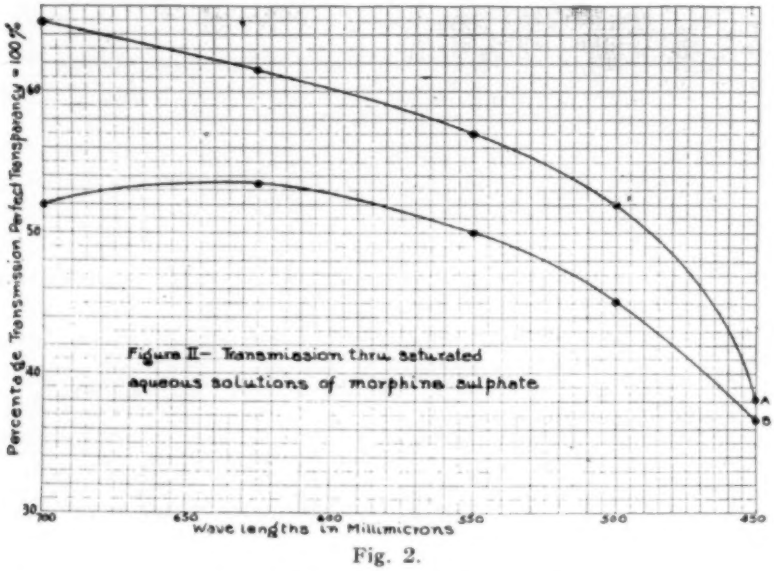


Fig. 2.

either absent from solutions of brand A or present in smaller amounts. If, then, brand B is slightly less pure than brand A the question arises as to why the solid brand B appears the whiter of the two.

Individual crystals of morphine sulfate, when examined under the microscope, of course, appear colorless. The market cubes are formed by compressing together a countless number of small crystals. They appear white only because each cube has myriads of small crystal faces from which light of all wave-lengths is reflected. Their whiteness is the same as the whiteness of snow which is composed of crystals of ice, each one of which, if inspected singly, is clear and not white.

From this it follows that the finer the average size of the individual crystals in the cubes the whiter the cubes should appear, all other things being equal. Microscopic inspection of the crystals of both brands showed that both were composed of crystals of widely different sizes. Brand B, however, was seen to have a greater percentage of finer crystals than brand A. In making up the solutions for the

transmission studies, the rates of solution were also found to be in this order; *i. e.*, brand B was completely dissolved considerably before brand A. It is evident, then, that brand B, which transmission curves show to be less pure than brand A, owes at least some of its slightly purer white appearance to the fact that the crystals of its cubes are, on the average, smaller.

Still further consideration of the curves of Fig. 2 shows that while there is an appreciable difference in the amount of light transmitted by the two solutions at the red end of the spectrum, both solutions transmit about the same amount of light at the violet end. In other words there is relatively more blue light passed by the solution of B than by the solution of A.

This lesser proportion of blue light transmitted by solutions of A can hardly be due merely to the presence of an impurity in A that absorbs blue light. As stated above, the total lesser transmission throughout the entire visible range indicates that solution B is the one that is the less pure morphine sulfate. The same effect could, of course, have been realized by adding a trace of a blue dye to product B. Such an addition would tend to offset a comparatively dirty, slightly yellow or brown color, making the absorption at all wave-lengths more nearly uniform. To the eye such a solution or solid would then appear more nearly plain gray than before, and if the crystals of such a product were finer the bulk solid could actually be made to look whiter than another product which is definitely the purer of the two.

The use of a blue dye to whiten materials of dirty color is, of course, common practice in the laundry. Although the presence of such a dye actually cuts down the total reflection of light, it does make the reflection throughout the entire visible range more nearly uniform. Hence, although the material is grayer than before, it appears whiter because the eye is more sensitive to differences in color than to differences in intensity of light in objects substantially white in color. Gray materials, of course, are merely those which reflect or transmit all wave-lengths equally but absorb some of all of them.

The evidence strongly suggests, therefore, that brand B morphine sulfate is contaminated by a trace of blue dye which aids in obscuring the dirty color which it otherwise would have because of impurities shown to be present by absorption studies. The whiteness of this product is also enhanced by the fineness of its individual crystals. Still other brands were examined, some of which owe their apparent slightly superior whiteness solely to the comparative fineness of the crystals of which they are composed.

We conclude, therefore, that it is unsafe to judge the purity of market brands of morphine sulfate solely by comparing the whiteness of the cubes in which form the various brands are usually marketed. All are naturally approximately white-appearing cubes to be marketable at all. The slight differences in the apparent purity of their whiteness may or may not be directly related to the chemical purity of the morphine sulfate in the cubes.

We wish to acknowledge the kindness of the Keuffel and Esser Company in placing at our disposal one of their Color Analyzers on which instrument the various color analyses alluded to above were made. The reflection measurements were made by gently crushing the cubes and packing the powder behind a plane glass window upon which white light could fall and be reflected back through the instru-

ment for analysis and measurement. The absorption studies were carried out on solutions contained in the 10-cm. tubes supplied with the instrument. The light emerging from these tubes was matched against the light from similar tubes filled with distilled water. Thus for both the reflection and the absorption measurements the differences between the various samples of morphine sulfate are significant rather than the absolute values.

MAKING YOUR NAME WORTH SOMETHING.*

BY ANDREW F. LUDWIG.[1]

I have often marveled at that strange complex of pharmacists which makes them seek to bury their personalities under an impersonal name. For instance, why does John Smith, pharmacist, present himself to the world as the Crescent Pharmacy, or the Broadfront Drug Company as the case may be? It seems incredible that either of these designations can have the same appeal, the same drawing power, or the same value, as the name of the pharmacist himself.

The whole thing seems all the more strange when it is recalled that everything underlying the existence of the Crescent Pharmacy revolves around the personal and individual attainments of the pharmacist himself. The pharmacist has been compelled to undergo an exacting period of training in order to fit himself for the practice of pharmacy and the operation of a drug store. The pharmacist has also been required to pass a State Board examination so that he, himself, may be declared competent to carry on the work for which he has prepared himself. In addition to all of this, he is dealt with on the basis of his personal qualifications and personal integrity in the matter of being licensed to deal in narcotic drugs. On all sides, and in all of his activities he is hedged about and controlled by what he personally and individually is and does.

In spite of this, when this same pharmacist comes to making a place for himself in the business world, a place in which he will exercise his personal talents and will make the public the beneficiary of his personal competency and skill, he blossoms forth under the thoroughly impersonal designation of the Crescent Pharmacy.

Not only does the Crescent Pharmacy become the name behind which the pharmacist loses his identity, but he resorts to the same means and methods when designating the prescriptions which he himself develops and prepares in consequence of his personal professional skill. The label which is placed on the prescription which he himself compounds, the product which permits him to make a professional reputation and build up a professional practice, also fails to carry his name.

The usual imprint line, in the event the store goes in for this type of preparations, is also developed under the name of the Crescent Pharmacy. Many pharmacists utilize imprint goods as a means of building up a business of their own. Products of this kind have no consumer appeal or consumer acceptance other than that which the pharmacist himself can give them. However, once these products become accepted the business in them belongs exclusively to the pharmacist himself. This is a type of professional pharmaceutical practice and, it would appear,

---

* Section of Commercial Interests, A. PH. A., Dallas meeting, 1936.

[1] Baltimore, Md.

their success would be greater if preparations such as this were developed around the personality of the pharmacist rather than under an impersonal title or designation.

I cannot conceive of "Lascoff's Pharmacy" being conducted under the name of the Lexington Pharmacy or the Lexington Drug Company. The store has become an internationally known institution simply because it has portrayed the professional attitude and point of view of the master pharmacist whose name it bears. While all cannot be "Lascoffs," the way is open to every pharmacist to develop his store around his personality, his personal skill and competency, and to establish a personal, professional reputation. In other words, every pharmacist is faced with an opportunity to make his name mean something!

PHARMACY'S POSITION UNDER REGULATED COMMUNITY MEDICINE.*

BY P. J. CALLAGHAN.

One of the great controversial questions of the day centers around the socialization of medicine; this subject was included in the Social Security Bill sponsored by the administration at Washington.

The American Medical Association is strongly opposed to socialized medicine in any form; the medical profession, however, is not unanimous in its opposition as there are certain sections of the United States in which health insurance is flourishing with the best doctors, hospitals and pharmacists included in the membership from which the patient may make his choice.

It is said that in some of the European countries where socialized medicine has been adopted the quality of medical care rendered under such systems is far below the average quality usually given in this country. The patient is likely to get scant consideration, is asked a few questions, handed a few pills or a bottle of medicine and told to come back later. He must take it and like it, as he has no choice in the selection of the doctor; this type of socialized medicine, it seems, would eliminate the pharmacist entirely.

The type of service rendered under the European plan is of such a standard that in Germany, for instance, when a person has a serious ailment he will go to an outside physician for treatment.

In England the doctors engaged in this type of practice are paid $2.00 a year per person; in order to enjoy an annual income of $2000.00 the physician must guard the health of 1000 people. Under similar regulations, what would a pharmacist's income be? I wonder. So much for socialized medicine as practiced in other countries. The point I desire to bring out is that in the European plan medication is furnished by the physician; the pharmacist is left entirely out of the picture.

Now let us consider what I shall call the American plan, namely, Health Insurance as practiced in Oregon and the state of Washington. While at the meeting of the N. A. B. P. in Portland last summer I met a gentleman who represented the Kings County Medical Service Bureau of Washington and the Multnomah Industrial Health Association. I was interested in the idea, it was some-

* Section on Education and Legislation, A. PH. A., Dallas meeting, 1936.

thing entirely new to me, and I asked him a great many questions which he answered gladly. He also gave me pamphlets with the lists of physicians, hospitals and drug stores available to the members of these associations. The entire cost of this service, including medicine, is $2.00 per month for the head of the family and 50 cents additional for each member of the family.

For this fee the member may choose from a list of 380 physicians and surgeons, and I was informed by a registered nurse that the list included the best members of the medical fraternity, fourteen hospitals, ambulance service, X-ray service and medicine.

I inquired about the medicines, their cost, etc. I was informed that as far as possible U. S. P. and N. F. preparations were used and after having a great many prescriptions filled an average price of 55 cents was arrived at.

Prescriptions are written in duplicate and on the back of the original is a list of the pharmacies at which they may be filled. The patient selects the pharmacist.

These so-called medical bureaus and health associations on the coast were started to offset the threat of socialized medicine under federal regulation as proposed in the Social Security Act. The physicians and pharmacists felt that if they must operate under a plan of socialized medicine they would prefer to make their own arrangements and have the plan in operation when and if federal regulation became a fact rather than wait and be told what to do, and how to do it, by a bureau at Washington. It is said that 500,000 persons are enrolled in health insurance groups at the present time.

The American system as practiced thus far at least holds some hope for the pharmacist, as he is not left entirely out of the scheme. A wave of health insurance activity may gain momentum enough to cause us some concern at some future time but my personal opinion is that the physicians, pharmacists and, last but not least, the American public will not stand for socialized medicine as we understand it and as it is practiced in some European countries.

This subject is of tremendous importance to the pharmacist of the United States, yet in trying to gather material for this paper I could not locate a single article on the part pharmacy would play in the scheme of socialized medicine; the editors of our journals have ignored the subject entirely.

Either the pharmacists do not know that the threat of socialized pharmacy exists, are indifferent to the situation or are afraid to bring the issue into the open; a frank discussion of this question in the meetings of the city, state and national bodies would tend to bring out facts which might be of great assistance in determining our future course of action regarding this important question, should the occasion arise.

PHARMACISTS IN THE BRITISH ARMY.

The committee of the British Pharmaceutical Society reported that they had received a report from Professor Gunn concerning conversations which had had suggesting directions in which the British War Office might be further approached on this question, and had remitted these proposals to a sub-committee for further consideration. The sub-committee had also been requested to examine the motion proposed by Mr. McNeal—"That a Corps of Pharmacists be established and trained in those duties which they would be called upon to perform in the event of war while serving with His Majesty's Forces."

EDUCATIONAL PROBLEMS IN PHARMACY.*

BY H. B. CAREY.[1,2]

There is an old saying, "It is only the fool who rushes in where angels fear to tread" which may be somewhat apropos and fitting for my suggestion of this subject for my talk to-day. From time immemorial to the present, all problems of education have provided a fruitful field for discussion and if I may venture a guess, they will ever continue to worry and annoy those who are charged with the responsibility of trying to guide the ship of pharmaceutical training in uncharted seas. At any rate, perhaps never in the history of Pharmacy has the subject given such concern to those of us who will be held responsible by future historians as it does to-day. Are we drifting toward the rocks enshrouded in fog, or are we facing the calm open sea with no compass and little if any knowledge of the stars and celestial regions? If you will excuse me for asking these questions, it will afford some consolation. Frankly, I am looking for advice and guidance.

MERCHANDISING VERSUS PROFESSIONAL PHARMACY.

The first question which requires answer will be, "Is Pharmacy a profession, a business or a merchandising racket?" The answer to this question must certainly be obtained if we are to make a curriculum and manage a College of Pharmacy. If chain, department stores and unscrupulous manufacturing houses continue to dominate and control and make it a merchandising racket, are we justified in trying to run colleges to furnish recruits who may give the semblance of respectability and semi-professional atmosphere? It seems to me that we have arrived at the time when a man who studies Pharmacy must agree and choose to make of this calling a profession rather than a very questionable business. If you want to find out for yourself, go into the nearest chain or department store and tell the clerk you want something for a lame back. If you get out without buying five or six dollars worth of worthless remedies it is because you lack the money. Some may say, to relieve the conscience, that it is not for us to worry about what the student does once he completes the work for his degree; that the training merely provides a means to earn a living.

STATISTICS.

Most of you will agree that we have two or three times more pharmacies or drug stores than we need. (At present (1) over sixty thousand in the U. S. A.) We have probably well over 200,000 persons who are licentiates, assistants and clerks in the United States. In California (2), we have over 3200 pharmacies and more than 12,000 licentiates and about twelve hundred registered assistants. It is perfectly evident we have no legitimate need for all of these people, the major portion of whom come from outside our state. (Yet we have much complaint that we do not recognize reciprocity.) Our own college, over a period of sixty-three years, has furnished approximately only 2300 graduates. The two Schools of Pharmacy in California last year added little more than a hundred graduates.

The present-day merchandising pharmacist cannot hope to obtain the confidence or respect of scientific medicine. If we do not soon provide a class of

* Abstracts from an address before the Section on Education and Legislation, A. PH. A., Portland meeting, 1935.

[1] University of California, College of Pharmacy.

[2] Deceased—see February JOURNAL, page 193.

educated persons who can meet the physician on an equal basis and counsel with him we shall, and rightly so, lose all contact with scientific medicine. The progressive manufacturing houses are going to the physician and doing for him the work which the well-trained and informed pharmacist should be doing. Many of these manufacturing companies do not hesitate to furnish samples and facilities recklessly. This encourages physicians to dispense them, and the samples frequently reach the patient who immediately calls for them by name and shops around for the lowest price.

Our future pharmacists, in my judgment, must be fully on a par intellectually with the physician and much better trained in Chemistry, Physics and Pharmacy. He should be regarded as a counselor and an advisor as well as a clever laboratory technician, especially skilled in Chemistry, Bacteriology, Serology, Pharmacology and Toxicology. The pharmacist of to-morrow must be a skilful artist and scientist in selecting, preparing, standardizing and dispensing of pharmacological remedies and his advice and counsel should be available just as that of the surgeon, the diagnostician or the radiologist. Medicine is not practiced, at least in the cities, without frequently calling in consultation well-known experts in specialty fields. There is no reason why the ideal pharmacist who is a thorough specialist in his chosen field may not some day in the near future enjoy this prestige and honor. He, at least, should be well able to convince the physician of the advantages of having his prescriptions carefully and skilfully filled. He should certainly have as much right to contact physicians as the big commercial and manufacturing concerns which find it very profitable to do so. Indeed, some of these well-known organizations give prizes or scholarships in medical schools and maintain a representative on the ground whose business it is to advise and acquaint students and practitioners constantly with their preparations. This should be a cue to the modern pharmacist who must by education and skill meet this competition and go it one better.

PROFESSIONAL PHARMACY.

It would appear, then, that only the professional pharmacist should in the future survive. He needs no expensive, high rent corner stores to meet the needs of legitimate medicine and pharmacy.

Is professional pharmacy possible? Will it come soon and who will sponsor it? These questions, I believe, must be answered by the College of Pharmacy. To-day we have, in my opinion, few Colleges of Pharmacy in the United States sufficiently well equipped and financed to carry this program to a successful conclusion. It costs money, plenty of it, to finance any high class technical and professional education. The states are to-day staggering under the great burden of taxes for public education. So long as people had income and money the majority were good spenders, especially for education and public betterment. In this reckless well-intentioned spending we have gone to the extreme of training farm work plugs for the race track—an absurd and senseless optimism. Education, like a machine, is only of value for the person who can use it.

LIMITATION OF ENTRANTS.

Have we arrived at the time where a Committee should be appointed to give information and advice relative to limitation of entrants to our Colleges of Phar-

macy? The raising of entrance and scholarship requirements will quickly do the required work but until intelligent coöperation of the profession of Pharmacy is obtained, we may expect little if any results.

In many countries of Europe, the number of pharmacies is automatically limited—depending upon the population. In some countries with each increase of six thousand inhabitants the establishment of a new pharmacy is permitted by the state. How much better it would be if we had some similar regulation.

FIVE-YEAR PLAN.

Some of our better Colleges of Pharmacy are anxious to extend the college training to a five-year period. Personally, I believe this will shortly come. With the junior colleges taking care of the two years of basic science work, this should not be an unreasonable or expensive requirement. In this program, the student could, if qualified, obtain his Masters Degree. In Universities which have Medical Schools, I believe a curriculum worked out jointly by both colleges leading to the field of Medical Technology and Toxicology has great possibility of usefulness for both professions. Many of the medical technicians at present are broken-down nurses or high school girls who require a meal ticket. These poorly and inadequately trained individuals are not qualified to render proper scientific service. The well-trained pharmacist should at once demonstrate his superiority in skilful technique and understanding.

EDUCATION.

Older pharmacists as a rule have never, at least in this country, received good and sufficient training to enable or encourage them to continue their studies after leaving college. At any rate, whether it was this quiz-compend training which they received or the worship of money, they quickly became fossilized. Intellectually they died shortly after graduation. The modern professional pharmacist must continue his studies after leaving college. He must attend his weekly and monthly scientific pharmaceutical, chemical and other allied educational meetings.

GRADUATE WORK.

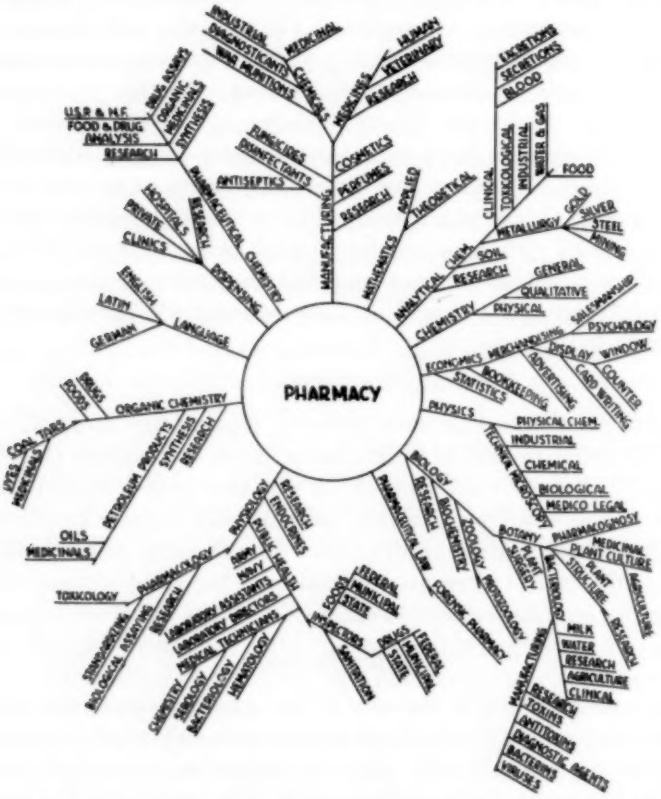
What are colleges doing in the way of free graduate meetings where the rank and file of Pharmacy might receive both information and inspiration and encouragement to keep abreast of the times? It is my judgment, and I have been intimately connected with Pharmacy for more than thirty-five years, that the rank and file of our profession is disgraceful in its backwardness; it is utterly lacking in all pretense to keep in touch with scholastic accomplishments and general improvements in methods and technique of the profession.

Professional Pharmacy must endeavor quickly to bridge the ever-widening chasm between medicine and pharmacy. It should leave merchandising pharmacy to the men of bygone days whose training does not fit them to carry on in modern scientific pharmacy. Professional Pharmacy should endeavor to find out whether the large manufacturing houses are friends or foes. If these large concerns are destroying the relationship between legitimate pharmacy and medicine it should be found out and the earlier the better.

The pharmacists of to-morrow must be investigators, interpreters and administrators. Without the investigator and the interpreter, pharmacy cannot hope to

succeed. Pharmacy in the scientific sense is an adjunct of medicine just as much as surgery, gynecology or pediatrics.

Medicine needs our skilled help in Chemistry, Physics, Biology and the arts. To render proper assistance our educational program must take into account the importance and necessity of the mastery of the fundamental basic sciences. The pharmacist of to-morrow should be better trained in the fundamentals of Physics and Chemistry than the physician, and he should aid the physician in his numerous problems. He must be able to correlate modern science of material things with the modern practice of medicine. For example, why should we recommend that



all our preparations for hypodermic and intravenous medication be buffered? How much do we know about the subjects of hormones, vitamins and endocrine glands, which play such an important rôle in our physiology? What does our biochemistry have to do with the preparation of foods and drugs? Why are Colloidal and Physical Chemistry being so greatly emphasized to-day? The secrets of science are slowly unfolding. Is it now time that we at least attend and witness these marvelous scientific shows, even if we are not able to play one of the leading rôles in the dramas of science?

The pharmacist of to-morrow must be able to do potentiometric titrations, biological as well as chemical assays, colloidal chemical manufacturing, and to determine physical and chemical properties to the nth degree of accuracy. He should be a scientific interpreter of pharmacological and physiological studies and experi-

ments. In short, he is the engineer who can furnish expert information and evaluation in the fields of pharmacological remedies.

PHARMACY A LIBERAL AND YET A PRACTICAL EDUCATION.

If you take the time to glance at the foregoing graph you will at once be impressed not only with the usefulness of the profession but with the numerous possibilities of allied specialties which can easily be developed. It is a blending of the theoretical and applied education which at once opens several avenues instead of one, which so often is the case in straight academic colleges. Many of our better students will quickly find their talents and go into fields remotely allied to Pharmacy. If they fail to make good in their specialties, they still have their profession of Pharmacy. Our well-balanced and well-presented pharmaceutical educational programs have, I believe, few equals for all around practical usefulness.

JUNIOR COLLEGES.

These relatively new institutions will, in the near future, play a very important rôle in our field of education. They can and must take over the burden of the first two years because the present average cost of tuition, $250.00 or $300.00 per year in Colleges of Pharmacy, is out of all normal proportion to the remuneration in the calling. Furthermore, a large percentage of our very worthy students cannot finance themselves, at least under present-day conditions. Unfortunately, many of the junior colleges are only mediocre high schools as far as equipment and faculty are concerned, and to make matters worse are badly overcrowded. The student will not be, at best, able to receive the University perspective which we so much appreciate and value. However, in due time these colleges may take on the University atmosphere and methods if entirely separated from high schools. If we, however, set up a good substantial curriculum and proper scholarship requirements, these will probably weed out a high percentage of hopeful but incompetent students who would enter the profession.

EMPHASIS ON BASIC SCIENCES.

In our California curriculum we have tried to emphasize the subjects which, in our judgment, will be most beneficial in laying a proper foundation for the superstructure of applied sciences which go to make up what we commonly call Pharmacy. It is further my belief that these subjects should be presented wholly as basic sciences without any reference to the possible application. The student should be taught, above all, to think, reason and understand. When he later comes to his application, he will continue to make use of these well-established educational methods.

REASONING VERSUS MEMORIZATION.

Here, may I pause a moment to express my disapproval of teaching in Colleges of Pharmacy where memorization is the main thing emphasized. This is further brought home to the student in the State Board Examinations which require only, in most instances, the memorization of an enormous number of antiquated cut and dried answers to questions in Pharmacy as it was practiced twenty to forty years back. This is an every-day picture which most of you see but rarely raise a

voice to correct. This weakness in our teaching and licensure methods is deserving of the most severe condemnation.

RATING COLLEGES OF PHARMACY.

The rating of the Colleges of Pharmacy is another subject which probably should not be mentioned. Who shall have the authority and how shall it be done? While the American Association of Colleges of Pharmacy is to be commended for all the good work which it has done in suggesting and encouraging improvement, it is not properly qualified to pass judgment upon its own members. Any attempt which does not take into account the following points is in our judgment quite incomplete:

1. Need for the college.
2. Personnel (faculty and students).
3. Equipment and buildings.
4. Financial support and endowments.
5. General morale.
6. Educational perspective as evidenced by the curriculum and especially the basic science foundation.
7. Productive work—research and general usefulness to the profession and the State.

It is regrettable we have not some qualified body or educational group capable of making such a survey of our American Colleges of Pharmacy and rating the same justly. It is quite obviously unfair to ask us to do our own evaluating. I venture to say that if such a survey were made by a qualified group of educators outside the profession, not more than 25% of the present-day schools would be considered adequate.

CONCLUSION.

In any great modern engineering problem every figure must be verified; all materials whether stone, sand, cement or metal must be tested, checked and double checked before the same may be accepted and used. Our problem, then, is one in engineering, so let us proceed with the methods and instruments of precision to carve out of this present-day chaotic mass called Pharmacy a *Profession*—built upon sound basic education which can weather the storms of adversity and scientifically serve the Medical Profession and the Public Health requirements.

REFERENCES.

(1) U. S. Census and Costs of Medical Care.
(2) California State Board of Pharmacy.

NOTE: *The passing of Dr. Carey, has presented difficulties in the publication of this paper; thanks are extended for the helpfulness of Dean T. C. Daniels, Dr. F. T. Green and the family of the deceased.*

KING GEORGE VI, PATRON OF THE BRITISH PHARMACEUTICAL SOCIETY.

KING GEORGE VI has consented to be patron of the British Pharmaceutical Society and British pharmacists hail the event as a most happy one and a recognition of the Society's long and honorable history. The Society celebrated the Coronation with a banquet in Guildhall on April 6th. The Lord Mayor of London was one of the speakers and prominent British pharmacists were well represented by more than eight hundred guests.

THE DEPARTMENT OF THE AMERICAN ASSOCIATION OF COLLEGES OF PHARMACY

ERNEST LITTLE—CHAIRMAN OF EXECUTIVE COMMITTEE, A. A. C. P., EDITOR OF THE DEPARTMENT.

Below are presented two papers of widely differing content and interest to our readers.

The first by Dr. Harris deals with a new course in "Plant Extractives" which has been introduced in the School of Pharmacy at the University of Oklahoma. It will be read with special interest by teachers of pharmacy and chemistry in our colleges of pharmacy. The chemistry of plant products is correlated with the student's study of plant extractives in a manner calculated to increase the student's interest and appreciation of such preparations.

In his paper "What Is a Shelf-Warmer?" Dr. Olsen has discussed a topic which is not new, but which is of fundamental interest to every retail pharmacist who is responsible for the management of a modern drug store. Dr. Olsen's conclusion is that in general "Shelf-Warmers" are found on the shelves of our drug stores not so much because the pharmacist purchases too great a variety of articles, but rather too many of one kind of any article. Customer demand will determine what should be found on the shelves of the drug store. Shrewd buying ability must see to it that these articles are not purchased in such quantities as to become "Shelf-Warmers."—ERNEST LITTLE.

THE USE OF CHEMISTRY IN TEACHING PLANT EXTRACTIVES.*[1]

BY LOYD E. HARRIS.

The students in pharmacy at the University of Oklahoma were being taught about fluidextracts, tinctures and extracts in a very perfunctory sort of way. That is, they started in with a definition of fluidextracts and then studied each of the preparations under this heading just as they were listed alphabetically. Naturally they forgot many of the facts that were presented in this manner. When they were called upon to fill prescriptions involving the use of this information, in the laboratory, they were frequently at a loss as to how to proceed.

As a result of the above conditions, a new course was introduced into the curriculum. These three classes of preparations, namely, tinctures, fluidextracts and extracts were separated from the other classes of galenicals that are usually taught in Operative Pharmacy courses. The name of the new course was "Plant Extractives." The prerequisites for the course were Pharmacognosy (Plant Drugs) and Organic Chemistry, in addition to the beginning courses in pharmacy. A knowledge of chemistry was believed to be essential for the proper approach of the subject matter to be presented. If you have not already done so, it is suggested that you read the article "Is Galenical Pharmacy a Science?" by Professor A. Tschirch. It appeared in volume 105 (1933) on page 441 of the *American Journal of Pharmacy*.

The first thing that is discussed in this course is the more common solvents that are used in pharmacy. The miscibility of each solvent with the others and mixtures of the others, together with their specific gravities, boiling points and viscosities are studied. This is followed by a discussion of solutions and the student is required to list in a note-book, the various classes of plant constituents that are

* Presented before the Chemistry Teachers Conference, American Association of Colleges of Pharmacy, Dallas, Texas, August 24, 1936.

[1] From the Pharmacy Laboratories, University of Oklahoma, School of Pharmacy.

soluble in each solvent. It is pointed out, under this heading, that each solution becomes a potential or possible new solvent.

In pharmacognosy, the student had learned about the distribution of the various classes of constituents in the plant and then in chemistry they had learned something about their properties. All of this is correlated and reviewed.

The students are next assigned some drug and they study its inorganic constituents. Moisture determinations are made in both the green and the cured drug. The importance of water in the growing plant, in the curing, storing and final extraction of the drug is emphasized. Enzymes, fermentation, etc., are especially emphasized. Ash determinations, including water-soluble, acid-soluble and insoluble ash, frequently give the student a new viewpoint as to the importance of inorganic salts in galenicals. Hydrogen-ion concentrations are also mentioned here.

The extraction of a drug, usually the same as used for moisture and ash determinations, by selective solvents is the next step. The modified Dragendorff method is employed. Using a continuous extractor or percolator, a convenient quantity of the sample is extracted with petroleum benzine and the amount of the extract or residue determined semi-quantitatively. At this time the student is given a series of experiments dealing with the physical and chemical properties of fats, volatile oils and mixtures of the two. As a library assignment, the definitions of the words and terms relating to them, such as soaps, saponification, spirit, etc., are required to be put into their note-books. The student also makes a list of all tinctures, fluidextracts and extracts that are made, using petroleum benzine, giving the reasons for its use.

The above extraction is continued, using the drug just extracted by the petroleum benzine and not a fresh sample, using ether as the next solvent. The same procedure is repeated that was used in the case of petroleum benzine. Thus they continue with alcohol, water, dilute acids and finally dilute alkalies. After water, the preparations made with alcohol-water menstrua are listed.

In the above classifications, that is according to the menstruum used, the student is asked to list the constituents that he believes to have been extracted by the specified solvents. This is done for all of the official preparations. Of course, he will not remember all of this data or information, but it does impress him with the general information.

The making of small quantities (two to four fluidounces of each) is then given some time and study. Finally the miscibilities or incompatibilities of a number of the preparations of these classes are tested. Their own preparations are used as far as is possible.

Thus the student has had a chance to learn something about the chemistry of plant products and to correlate this information with his study of plant extractives. This information gives him the ability to properly mix, if it is possible, two or more of such preparations if the need arises in prescription work. It also gives the student an appreciation of this class of preparations. A fluidextract or a tincture is no longer just another liquid to be poured from one bottle to another.

WHAT IS A SHELF-WARMER?

BY PAUL C. OLSEN.

About ten years ago, the Druggists' Research Bureau was formed under the direction of a committee of representatives of the American Association of Colleges of Pharmacy, the National Association of Retail Druggists and the National Wholesale Druggists' Association to collect and distribute facts about the business problems of pharmacy. When the committee first met there was immediate agreement that there were plenty of problems in retail pharmacy, but the question was their relative importance. Which one should be studied first?

In order to get a definite and worth-while answer to this question, queries were addressed to proprietors of retail drug stores of all types and sizes in all sections of the country. From the 2500 replies received, it was evident that the overwhelming majority of these drug store proprietors were convinced that stock control was outstandingly first in the harassing and involved business problems of retail drug stores. That illustrates how important is this question of, "What is a shelf-warmer?" because when a druggist says that stock control is an outstanding problem in his store, what he means is that he has trouble in having in his store the kind and quantity of merchandise that his customers want to buy. You can put the question the other way round by saying that drug store proprietors have trouble in determining what kinds of merchandise to stock in their stores.

Because of this very evident interest in stock control, or to put it in the form of the title of this paper, the interest in "What is a shelf-warmer?" the question was pursued further by the Druggists' Research Bureau. Drug store proprietors were not asked how many shelf-warmers they had in their stores. That is like asking a woman whose favorite literature is the confession and love story magazines, what magazine she reads. She would be likely to reply, "*Scribners* and *Atlantic Monthly*" just for the impression that it makes.

Accordingly, the question to drug store proprietors was phrased in the following manner. Of the stock of the following items which you have in your store, which ones will you reorder when present stocks are exhausted? Then followed a list of several important classes of cosmetic and toilet preparations sold in drug stores.

When the results of this investigation were compiled, it was found that less than one-fifth of the merchandise stock that these several thousand drug store proprietors had on hand, was merchandise that they said they would reorder when present stocks were exhausted. That meant, of course, that four-fifths of the money they had tied up in their merchandise stocks was composed of shelf-warmers. Again, we have an illustration of how important is this question of "What is a shelf-warmer?"

When such facts as these are brought to the attention of drug store proprietors, a common question is, do you recommend throwing away four-fifths of a drug store's stock? Certainly not. To be more specific, if a good customer asks for an item which is not in stock in the store, the proprietor should offer to obtain it for her. He should endeavor always to have in his store the different kinds of merchandise which his customers want to buy. The stock of a well-managed drug store is

bound to be constantly changing in extent and variety. Shelf-warmers do not result from the practice of such a policy. They come from entirely different sources.

One of the most important of these prolific sources of shelf-warmers is the high pressure salesman who says, in effect, "Doctor, you can't make any money selling national brands at cut prices. What you need is a private brand with your own label on it on which you can get your full profit."

I have no objection to national brands nor to private brands, but I do say with all the emphasis at my command that national brands or private brands which are unsalable in a particular drug store are certain to become shelf-warmers. In the case just cited, the contagious enthusiasm of the salesman may communicate itself to the proprietor, with the result that he may sell a package or two of the private brand but, try as he will, the rest of the huge quantity purchase necessary to get his own label on the private brand gathers dust and becomes a shelf-warmer.

Another important source of shelf-warmers is the unwarranted enthusiasm with which some drug store proprietors embrace new items. This statement may seem to be contrary to the one I just made above in which I suggested that drug store proprietors should aim to have all the new items in stock for which there is demand in their communities. I did say that. I say now that the shelf-warmers result not from the purchase of such items, but from the purchase of them in unwarrantedly large quantities. A call once a week for an item is no justification for buying that item in three-dozen lots, as I have seen happen frequently. A quarter-dozen purchase is probably all that is justified and, at the beginning, a quarter- or a sixth-dozen purchase is probably the wiser policy.

Thus, in answer to the question which is the title of this paper, we reach the conclusion that shelf-warmers in drug stores result, for the most part, not so much from the great extent and variety of the stock in drug stores to-day, but from the purchase of excessive quantities of items of unproved or uncertain salability.

FOSTER LECTURE FUND AT UNIVERSITY OF BUFFALO.

Receipt of a gift from Mrs. Orrin E. Foster of Buffalo to establish and endow a permanent lecture foundation in chemistry and allied sciences has been announced by Chancellor Samuel P. Capen.

The new foundation, which will be known as "The Orrin E. Foster Lecture Fund," was pledged by Mrs. Foster, in the University's endowment campaign of 1929, as a memorial to her husband, the late Orrin E. Foster. Long-time friends of the University, Mr. Orrin E. Foster and his family were the donors of Foster Hall, which was the first new building to be erected on the North Main Street Campus. Dedicated on October 27, 1922, in connection with Chancellor Capen's inauguration as head of the University, Foster Hall has already seen 15 years of service as a laboratory for chemistry and pharmacy students and has become the northeast corner of the new Campus quadrangle.

Since income from the new bequest is now available, plans have been completed to inaugurate the foundation at once, with a series of public lectures, beginning in March. Four of the lecturers and their subjects are as follows: Dr. Karl K. Darrow of the Bell Telephone Laboratories of New York City, "Atoms and Elements;" Dr. Marston T. Bogert, Professor of Chemistry at Columbia University, "Around the World in Search of Perfumes;" Dr. Frank C. Whitmore, Dean of Physical Sciences at Pennsylvania State College and president-elect of the American Chemical Society, "What Do the Organic Chemists Really Know?"

PROCEEDINGS OF THE LOCAL BRANCHES

"All papers presented to the Association and Branches shall become the property of the Association with the understanding that they are not to be published in any other publication prior to their publication in those of the Association, except with the consent of the Council." —Part of Chapter VI, Article VI of the By-Laws.

ARTICLE III of Chapter VII reads: "The objects and aims of local branches of this Association shall be the same as set forth in ARTICLE I of the Constitution of this body, *and the acts of local branches shall in no way commit or bind this Association, and can only serve as recommendations to it.* And no local branch shall enact any article of Constitution or By-Law to conflict with the Constitution or By-Laws of this Association."

ARTICLE IV of Chapter VII reads: "Each local branch having not less than 50 dues-paid members of the Association, holding not less than six meetings annually with an attendance of not less than 9 members at each meeting, and the proceedings of which shall have been submitted to the JOURNAL for publication, may elect one representative to the House of Delegates."

Reports of the meeting of the Local Branches shall be mailed to the Editor on the day following the meeting, if possible. Minutes should be typewritten with wide spaces between the lines. Care should be taken to give proper names correctly and manuscript should be signed by the reporter. *Please advise us of changes in Roster and mail reports promptly.*

BALTIMORE.

The March meeting of the Baltimore Branch, AMERICAN PHARMACEUTICAL ASSOCIATION, was held on Thursday, March 11, 1937, at the School of Pharmacy Building, University of Maryland. Due to the death of his brother a day or so previously, President Hewing was unable to be present, and this meeting was called to order by Vice-President John C. Bauer. Twenty-seven members attended.

The guest speaker on this occasion was Samuel L. Hilton of Washington, D. C.; he reviewed some of the developments and advances made in pharmacy during the long period covered in his active career as a professional pharmacist, with especial reference to the part played by retail pharmacists in the advances noted.

In commenting on the changes and improvements made in the type of pharmaceutical products made available for use by physicians in the treatment of disease since the beginnng of his experience, the speaker recalled that the first coated pills made available commercially in this country were coated with varnish instead of gelatin, and were almost insoluble when administered. A Polish pharmacist who operated a pharmacy in Washington was credited with being the first to suggest a method of manufacture which produced a soluble pill of much better appearance, but showing the pin-hole imperfections long familiar to older pharmacists. Following the early pills came the concentrated liquid extracts known as fluidextracts, which were so widely used but of doubtful therapeutic value in many cases due to a lack of either chemical or biological assays to determine their potency. Early progress of the evolution of the present-day elegant and therapeutically effective drug products was necessarily slow due to a lack of knowledge regarding drug constituents, and the further fact that most of the early improvements had to be worked out by individual pharmacists in the prescription department of retail drug stores.

The speaker stated that changes and advances in pharmacy during the past 25 years had been so numerous and rapid that it was almost impossible for a pharmacist to keep abreast with them. He attributed most of this more recent advance to the great strides forward made in organic chemistry, and the numerous research workers now directing their efforts to the improvement of pharmaceutical products.

The thought was advanced that the day is not far distant when retail pharmacists will be compelled to have more and better pharmaceutical equipment in order to supply the needs of physicians. The pharmacist should be equipped to carry out sterilization processes, to prepare accurately all kinds of reagents and stains required by physicians for office use, and be prepared generally to provide the type of service which physicians have a right to expect of the pharmacist as representative of a profession. He advised close coöperation with physicians in such public health matters as the control of habit-forming drugs and hypnotics.

At the close of this address the speaker was offered a rising vote of thanks by the members present. His remarks had aroused a responsive interest in his hearers, as was evidenced by the

desire of a group of members to hear further comments on topics discussed. Dr. H. A. B. Dunning was prevailed on to provide some further discussion.

In the extemporaneous talk by Dr. Dunning some of the points made by Dr. Hilton were heartily seconded. The attitude of many younger pharmacists who regard experimental work in general as alien to the prescription counter was deplored by the speaker. He maintained that with the advantage of a well-rounded pharmaceutical education the younger generation of pharmacists had very much greater opportunities for the advancement of pharmaceutical knowledge and practice than had those older men whose persistent efforts with meager equipment had contributed so much. The every-day work of a prescription pharmacist brings up many problems, the solution of which may well lead to important discoveries or to worth-while advances in the art of practical pharmacy. In any event the important matter of compounding potent drugs for the relief of human suffering or the saving of a human life certainly demands the best efforts of which any right-minded pharmacist is capable.

After the meeting a short social session was held with refreshments being served.

R. S. FUQUA, *Secretary.*

CHICAGO.

The Chicago Branch was highly honored on the 23rd of March by having as guest and speaker Dr. George D. Beal, president of the AMERICAN PHARMACEUTICAL ASSOCIATION.

A dinner was held at the West Side Professional Y. M. C. A. at which sixty-three members and friends attended. During dinner entertainment was furnished by two of the students from the Pharmacy College with vocal and accordian renditions.

Among those present at the dinner were George Moulton, president of the National Association of Boards of Pharmacy, H. C. Christensen, former president of the A. PH. A. and secretary of the National Association of Boards of Pharmacy, Prof. E. N. Gathercoal, Chairman of the Revision Committee of the National Formulary and president-elect of the A. PH. A.; Wm. Gray and I. A. Becker, hospital pharmacists, R. A. G. Linke; Drs. Lanwermeyer, Struth and Taburn of the Abbott Laboratories, George L. Secord and O. U. Sisson, well-known local druggists and many of the instructors and their wives from the Pharmacy College.

After dinner the members retired to the lounge room where about two hundred and fifty assembled to listen to Dr. Beal's discussion of "Science in Industry."

Dr. Beal began his discussion with the question, "What is pure research and what is applied research?" He stated that applied research must have some immediate value and application. In the application of research the various sciences are interdependent.

Until about the last decade research was considered a luxury but during the depression, in particular, it was noted that those companies that forged ahead were those who had faith in their research departments and gave them hearty coöperation. Many new industries arose during the depression period.

The cellulose derivative industry was cited as an outstanding example of progress and of new industries born through research. The evolution of bread making by large bakeries, supplanting home baked bread, was given as another example of applied research. Many obstacles had to be overcome such as wrapping for cleanliness and freshness, improved wrapping with cellophane and then sliced bread. These evolutions in industrial progress are examples of directed research based upon a careful study of what the consuming public desires.

Much research is done from industrial necessity. Cheaper sources of materials are demanded, by-products that are poisonous must be treated or overcome, new uses must be found for saturated markets, by-products may be developed into new industries of their own. As examples: the slag from the steel mills is now used to make Portland cement, the objectionable sulfurous fumes from the steel mills are converted into sulfuric acid, the arsenic in the fumes is recovered and used as an insecticide.

The problem of smoke coming from the large industrial plants using soft coal as fuel was discussed. This smoke contains sulfur fumes which are converted into sulfuric acid, the sunlight is screened, many materials are soiled and corroded and fine particles of carbon are in the air. This can be overcome by controlling those plants already in operation and by insisting that all new plants be so constructed as to eliminate the evil and for domestic use have centrally located heating plants using specially treated fuel.

The passing of the destructive distillation of wood as a major industry due to research having found cheaper methods of producing wood-alcohol, acetic acid and acetone is an example of chemical industrial evolution that is taking place. The naval stores who handle rosin, turpentine, pine oil and pine tar have been put on their toes due to competition. Laboratory studies have shown that turpentine has certain specific advantages as a paint thinner. The naval stores have also done a certain amount of market research to increase the sale of their products.

Granulated table sugar is one of the cheapest organic chemicals that one can buy. This suggested its use as a raw material in chemistry.

Sugar is an alcohol and will form esters. Sucrose and acetic anhydride will produce sucrose octa-acetate. It is now used as a plasticizer and as an adhesive for cellophane. Its bitterness was noted but no particular attention was paid to it until the government issued regulations requiring its inclusion in all rubbing alcohol. This unexpected stroke of fortune was like manna from heaven for the company that had been struggling along manufacturing it and trying to increase its uses.

Science is the fact finding agency of industry, it finds new materials, processes and uses. The organization behind the research must have faith in it and support it if results are to be obtained.

The aim of all research is to produce more comfort and convenience for the human race.

The most important thing in the training of research specialists is to obtain soundness and breadth in the fundamentals of the subject. Breadth of training helps a man as no promise can be made of life time employment in the same field due to changes and developments that may take place.

The evolution of the packaging of coffee was discussed. Of pharmaceutical importance is the fact of the discovery that the cells of the coffee bean are broken down by pressure, making extraction by percolation quite rapid. There is the possibility that this process might be applied to plant drugs to aid in their extraction.

The case of improvement in water purification to lessen boiler scale was elaborated upon to show the results of directed research and of implications that were taken advantage of in the work. The chemists wanted to find a method of bringing down the insoluble carbonates of "boiler scale" as an easily removable mud. They cast about and found that it should be a phosphate. After experimentation sodium metaphosphate was produced and found to form a double salt of sodium and calcium metaphosphate that was soluble. After mastering this problem they cast about for other applications of this phenomena. The metaphosphate was buffered with Sodium Sesquicarbonate and is now used to treat water for laundry purposes, the scouring of wool, and has many practical uses in the home where a soft water is desirable.

As a résumé, the research specialist should satisfy the following conditions; he should have a good fundamental training, should be well read, know how to find information, should have an imagination, be ingenious, have foresight, be systematic, observe and record facts, should follow hunches, must know how to create a demand for his products, must be diplomatic, cooperative with fellow workers, patient, and must be able to work with all types of people.

A rising vote of thanks was extended to President Beal for his very interesting and stimulating discussion.

The meeting was adjourned by President Morrison and was followed by many group discussions and pleasantries.

LAWRENCE TEMPLETON, *Secretary.*

NEW YORK.

The March meeting of the New York Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held March 15, 1937, in the Columbia University, College of Pharmacy, New York City.

About fifty members and guests were present.

The minutes of the February meeting were read and approved.

Treasurer Currens reported a balance on hand of $445.88.

Chairman Lehman, of the Committee on Education and Legislation, reported as follows:

"The most interesting and encouraging report is the news that the Court of Appeals has

rendered a decision that the non-signatory clause of the Feld-Crawford Law was valid. This is the clause which originally was declared invalid.

It will be necessary and advantageous to the twenty-seven states having Fair Trade Laws to have the Tydings-Miller Fair Trade Enabling Act passed, as such a statute will make the enforcement of the provisions of Fair Trade Legislation much simpler and more effective. All pharmacists are urged to write to their Senator and Congressman to favor the bill when it comes up to vote.

The Committee on legislation of the N. Y. State Pharmaceutical Association has had, up to a few weeks ago, a lively time in Albany; however, legislation has been somewhat tied up by the deadlock in the Senate. This will be broken after April first when a new member will be elected to fill a vacancy caused by a death.

The bills favored by the New York State Pharmaceutical Association are (in the Senate):

Int. No. 35, Senator Williamson, in relation to the misrepresentation of newspapers and periodicals.

Int. No. 82, Senator Feld to protect trade mark owners: same as Feld-Crawford Act passed in 1935. Now unnecessary on account of Court Decision.

Int. No. 481, Senator Twomey, this bill would relegate the sale of all drugs and medicines to places licensed by the Board of Pharmacy.

Int. No. 483, Senator Twomey, to define the word Chemist in Art. 51 of the Education Law.

Int. No. 484 Senator Twomey, in relation to registration of Pharmacies.

Int. No. 487, Senator Dunckel, restricting the sale at wholesale of poisonous, deleterious and habit-forming drugs to licensed dealers only. Also a State Robinson-Patman to be introduced by Senator Feld as soon as possible.

BILLS OPPOSED IN THE SENATE.

Int. No. 249, Senator Doyle, in relation to the preparing and serving of food in pharmacies.

Int. No. 250, Print No. 256, Senator Doyle, in relation to the regulation of Soda Fountains and Restaurants operated in connection with drug stores and pharmacies.

Int. No. 594, Senator Esquirol, creating a consumers' bureau in the State Department of Health.

Int. No. 67, Senator McNaboe, increasing the powers and activities of the Bureau of Narcotics of the State Department of Health, duplicating the Harrison Narcotic Act.

BILLS FAVORED IN THE ASSEMBLY.

Int. No. 339, Assemblyman B. J. Moran, a Robinson-Patman measure.

Int. No. 414, Assemblyman Lavery, The Feld-Crawford Law.

Int. No. 654, Assemblyman Piper, same as Senator Twomey 484.

Int. No. 922, Assemblyman Armstrong, same as Senator Twomey, 483, defining the word Chemist.

BILLS OPPOSED IN THE ASSEMBLY.

Int. No. 268, Assemblyman Langenbacher, same as Senator Doyle 250, regulating fountains and restaurants in drug stores.

Int. No. 269, Assemblyman Langenbacher, same as Senator Doyle 249, against serving of food in pharmacies.

Int. No. 982, Assemblyman Neustein, health insurance.

Int. No. 928, Assemblyman Holley, same as Senator Esquirol 594, in reference to creation of a consumers' bureau in the State Dept. of Health.

Bulletin of the N. Y. Pharmaceutical Council warns against the sale of paraldehyde without prescription: inspectors are attempting to induce pharmacists to sell same over the counter.

The Council has appointed a number of the members to act upon the Advisory Committee on Venereal Diseases Control of the Dept. of Health. The purpose of the committee is to work with the Dept. of Health in relation to all matters pertaining to the control of venereal diseases.

The Board of Directors of the N. Y. Pharmaceutical Council declares itself in favor of a modified NRA.

Motion was made by Dr. Lascoff that the report be accepted and the thanks of the Branch be extended to Mr. Lehman for his work. Motion was passed.

The secretary reported that the joint conference of the National Association of Boards of Pharmacy and the National Association of the Colleges of Pharmacy had been very successfully held on Monday and Tuesday, March 8–9, 1937, at the Hotel Pennsylvania. The Banquet and Entertainment held on Monday evening was a social success and through the kindness of the Mallinckrodt Chemical Co., who acted as hosts for the visiting delegates, was also a financial success.

Frank Berman, a member of the Association, offered by letter a plan for the "Creation of a Pharmaceutical Unit in Health Departments of Various Political Subdivisions of the United States."

This plan is submitted to the Commissioner of Health of the City of New York for suggestions as to feasibility, modifications—substitution or approval, for the purpose of presenting a final plan to the AMERICAN PHARMACEUTICAL ASSOCIATION as a model for other Health Departments.

HEALTH DEPARTMENT PHARMACEUTICAL SERVICE SHALL CONSIST OF THE FOLLOWING UNITS AND SERVICES.

1. Analytical Laboratory Service

2. Inspection Division

   To inspect pharmaceutical and chemical establishments for the purpose of:
   - (*a*) Getting samples to test for strength and purity
   - (*b*) Cleanliness
   - (*c*) To check on the eligibility of the personnel to practice and notify the State Board of Pharmacy of violations
   - (*d*) To detect the sale of prohibited drugs and articles
   - (*e*) To check on record of registration of nonofficial preparations not containing the formula printed on the label thereon

3. The Clinical Service

   - (*a*) Putting assistant grade registered pharmacists in charge of large active clinics
   - (*b*) This will insure competent dispensing service
   - (*c*) Intelligent requisitioning
   - (*d*) Necessary compounding on the premises
   - (*e*) Prevent shortages and overstocking

4. The personnel and duties

   - (*a*) A central administrative staff functioning through
   - (*b*) Pharmacist inspectors
   - (*c*) Pharmacist in the assistant grade as clinic pharmacists
   - (*d*) Laboratory pharmaceutical service
   - (*e*) Supply and equipment station pharmacists to facilitate distribution.

The pharmacy service shall be filled by civil service exams and transfers from other departments and promotions. Submitted by Frank Berman, Pharmacist, Department of Hospitals of N. Y. City with the collaboration of Louis Harris of same department.

After hearing the plan, Dr. Wimmer remarked that inasmuch as the plan involved a reorganization of the Health Services of the City and as the plan would take away some of the functions of the State Board of Pharmacy, it was a matter for the consideration of the N. Y. Pharmaceutical Council, the latter being more representative of pharmacists as a whole in New York. He moved that the secretary refer Mr. Berman to the Council. Motion seconded and carried.

Chairman H. V. Arny, of a special committee, presented the following:

DR. GEORGE C. DIEKMAN

The New York Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION has suffered a great loss in the passing of our past-president.

Dr. George C. Diekman departed from this life on January 30, 1937.

Graduate of the New York College of Pharmacy, Class of 1888; Professor of Pharmacy at the College, 1891–1927; member of the Board of Pharmacy, both City and State, from 1895 to 1937; Dr. Diekman has served Pharmacy of the city, state and nation faithfully, intelligently and unselfishly. His interest in his *Alma Mater* was so unflagging that it is proper to acclaim him as its most devoted son.

It is therefore appropriate to enter upon our minutes these

Resolutions of Sorrow.

Resolved, that this Branch register its profound sorrow over the passing of our beloved past-president, Dr. George C. Diekman.

Be It Further Resolved, that a copy of these resolutions be conveyed to his widow and daughter with expressions of our sincere sympathy.

NEW YORK BRANCH AMERICAN PHARMACEUTICAL ASSOCIATION.

President Schaefer then introduced Dr. James C. Munch, who addressed the meeting on the subject of "Pharmacology for (Graduate) Pharmacists."

CHARACTERISTIC ACTIONS OF IMPORTANT DRUGS.

Name.	External Action.	G. I. T.	Nervous System.	Circ.	Resp.	Muscles.	Endocrines.
Phenol	A	+	−	−	−	−	−
Salicylates	A	+	D	?	−	−	−
Cascara	−	+	−	−	−	−	−
Castor Oil	−	+	−	−	−	−	−
Ipecac	+	+	−	−	−	−	−
Mg Salts	−	+	D	−	−	−	−
Alcohol	+	D	D	D	+	D	+
Barbiturates	+	D	D	−	D	D	−
Belladonna	+	D	D	+	S	−	−
Bromides	+	+	D	−	−	−	−
Caffeine	−	+	S	+	(D)	+	+
Chloroform	A	D	D	(D)	(D)	−	+
Cocaine	+	D	D	−	(D)	?	−
Ephedrine	−	−	S	−	(D)	S	−
Epinephrine	+	−	S	(D)	(D)	−	+
Opium	+	D	D	+	(D)	S	−
Physostigmine	−	S	S	+	(D)	S	−
Strychnine	−	−	S	?	(D)	+	−
Digitalis	−	+	S	D	−	−	+
Nitrites	−	−	+	D	−	−	+
Insulin	−	+	−	−	−	−	−
Pituitary Ext.	−	S	−	+	−	S	S
Thyroid	−	S	S	−	−	−	−
Ergot	+	S	D	+	−	S	−
Quinine	−	S	+	−	−	−	−

D = depress, S = stimulate, A = antiseptic, + = definite action, − = no significant action and ( ) = toxic dose.

1933 SURVEY DATA RECALCULATED TO FREQUENCY PER 10,000 PRESCRIPTIONS.

850.

CODEINA.

400–500.

ACIDUM ACETYLSALICYLICUM
PHENOBARBITALUM
SODII BROMIDUM

300–400.

Acetphenetidinum
Pepsinum
Sodii Bicarbonas

200–300.

Acidum Boricum
Ammonium Chloridum
Argento-Proteinum
BELLADONNA
CAFFEINA
CASCARA SAGRADA
DIGITALIS
EPHEDRINA
Glycerinum
MORPHINA
NUX VOMICA
OPIUM
PHENOL
QUININA
SODII SALICYLAS
STRYCHNINA

100–200.

ACIDUM SALICYLICUM
Aminopyrina
Bismuthi Subcarbonas
Bismuthi Subnitras
Camphora
COCAINA
EPINEPHRINA
Ferri Chloridum
Gentiana
HYOSCYAMUS
IPECACUANHA
MAGNESII OXIDUM
Mentha Piperita
Menthol
Phenylis Salicylas
Potassii Citras
Potassii Iodidum
Prunus Virginiana
Sodii Benzoas
Terpeni Hydras
THYROIDEUM
Tolu
Zinci Oxidum
Zinci Sulfas

50–100.

ÆTHYLMORPHINA
ALCOHOL
Antipyrina
Cinchophenum
ERGOTA
Hydrargyri Chloridum Mite
Hydrargyrum Ammoniatum
Iodum
Methenamina
Petrolatum Liquefactum
Phenolphthaleinum
Potassii Arsenas
Potassii Bromidum
Renninum

10–50.

Acacia
Acetanilidum
Aconitum
ÆTHYLIS NITRIS
Aether
Aethylis Aminobenzoas
Aloe
Arseni Trioxidum
BARBITALUM
Bismuth Subgallas
Cannabis
Cinchonidinæ Sulphas
Chloralis Hydras
CHLOROFORMUM
CINCHONA
GLYCERYLIS NITRAS
Glycyrrhiza
Hydrargyri Chloridum Corrosivum
Homatropinæ HBr
Liquor Ergosterolis Irradiati
MAGNESII SULPHAS
Neocinchophenum
Oleum Morrhuæ
OLEUM RICINI
Oleum Menthæ Piperitæ
Potassii Acetas
Rheum
Scopolaminæ HBr
Sodii Chloridum
Sodii Citras
Sodii Iodum
Sodii Phosphas
Strontii Bromidum
Theobromina

1–10.

Arseni Iodidum
Bismuthi Subsalicylas
Cantharis
Hyoscyaminæ HBr
Iodoformum
Magnesii Citras
Neoarsphenamina
PHYSOSTIGMINA
Procaina
Santoninum
Theophyllina

Less than 1.

Arsphenamina
INSULIN
PITUITARIUM

Dr. Munch presented a list from the 1933 survey recalculated to show the frequency per 10,000 prescriptions. District No. 2 of the National Association of Boards of Pharmacy and of

the National Association of Colleges of Pharmacy lists 427 drugs for examination and study purposes. Supposing there are 10 things to learn about each of these, it figures out that about eight minutes can be devoted to each drug in the usual college course. The frequency table shows that many of these are not in sufficient use to demand extensive study of the pharmacy student. It would be better to know twenty-five drugs completely than to know 1000 improperly. A list of twenty-five drugs which are considered important are presented. Dr. Munch then discussed each of these in some detail.

After considerable discussion the speaker was accorded a rising vote of thanks and the meeting adjourned.

HORACE T. F. GIVENS, *Secretary*.

PHILADELPHIA.

The February meeting of the Philadelphia Branch, AMERICAN PHARMACEUTICAL ASSOCIATION was called to order by President L. L. Miller, February 9th, in the Auditorium of the Philadelphia College of Pharmacy and Science.

The minutes of the previous meeting were read and approved.

The secretary read the proposed amendment to the By-Laws: Its adoption was moved and seconded and a unanimous vote was received. Thus the fiscal year of the Philadelphia Branch shall be from January first of one year to December 31st of the same year. The change to apply to the collection of dues only.

James C. Munch proposed the name of Dr. Herbert Cobe for membership. Applicant was unanimously voted into membership.

President Miller appointed Dr. Frank H. Eby to audit the Treasurer's books and report on same at the next meeting.

President Miller appointed the following Nominating Committee: *Chairman*, James C. Munch, A. B. Nichols and Ambrose Hunsberger. The Committee is to report at March meeting.

The speaker of the evening, C. R. Addinall, director, Library Research, Merck & Co., gave a most interesting lecture on the subject, "Recent Advancements in Synthetic Chemistry." The lecture covered "Vitamins," "Cholines," "Plant Hormones" and the recently publicized "Prontosil." He emphasized the enormous quantity of literature that has appeared on vitamins. He discussed the formula of Vitamin B and told how it had been isolated in pure form from rice and how it was being prepared synthetically at a very reasonable price.

Lantern slides demonstrated the speaker's remarks on "auxin," plant hormone. Prontosil was discussed at some length as to its structure and synonyms. No claim was made for its value.

Motion pictures concluded the meeting.

GEORGE E. BYERS, *Secretary*.

MARCH.

The March meeting of the Philadelphia Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held at Mitten Hall, Temple University, on Tuesday evening, March 9th.

Minutes of the February meeting were read and approved.

The treasurer's annual report was submitted with a certificate of audit by Frank H. Eby and showed a balance in the checking account of $204.26, as of March 3, 1937. The segregated savings account showed a balance of $49.84 as of the same date. Treasurer Byers reported $117.00 outstanding as uncollected dues. The treasurer further mentioned that certain delinquent members had been dropped from the list because of their failure to pay dues over a period of two years. He emphasized that the mailing of notices is an expensive item and that since certain members have failed to either pay dues or attend meetings over the above-mentioned period of time, their names have been removed from the active files, thus accounting for the failure of certain individuals to receive notification of meeting dates.

James C. Munch, of the Membership Committee, presented the names of W. J. Boegly and G. W. Drain for membership in the Local Branch. A motion was made and carried that these men be elected to membership upon payment of the usual contribution. These names brought the total of new members to 14 for the year.

Other committees having nothing to report, President Miller dismissed all standing committees with thanks for their coöperation and assistance during his term of office.

President Miller then introduced the speaker of the evening, Dr. John C. Krantz, professor of Pharmacology in the Medical School of the University of Maryland. He spoke on the subject, "Discovery, the Increment of Progress." Attacking the subject from three angles the speaker outlined the developments which have aided man most in his fight for the alleviation of pain; the development of the science of Antiseptology and Chemotherapeusis; and the development of the science of Endocrinology.

Following his address the speaker was accorded a rising vote of thanks.

President Miller called for the report of the Committee on Nominations. Chairman Munch presented the following nominations: *President*, H. Evert Kendig; *First Vice-President*, S. H. Kerlin; *Second Vice-President*, Geo. E. Byers; *Secretary-Treasurer*, A. K. Leberknight; *Delegate to House of Delegates*, Ambrose Hunsberger.

There being no nominations from the floor, a motion was made and carried instructing the secretary to cast the ballot as submitted.

President Miller expressed his appreciation for the support and coöperation of the retiring officers and the membership as a whole.

The newly elected president was then introduced to the meeting by the retiring president. President Kendig responded with a short address and then introduced the other new officers, each of whom responded briefly.

On motion by Ambrose Hunsberger a rising vote of thanks was extended to the retiring officers.

Previous to the meeting the annual Past-President's dinner was held in the faculty dining room in Mitten Hall and was attended by the following Past-Presidents: William Pearson, E. Fullerton Cook, Ambrose Hunsberger, Adley Nichols, J. W. E. Harrisson, James C. Munch, W. J. Stoneback, Frank H. Eby and B. C. Goodhart.

ARTHUR K. LEBERKNIGHT, *Secretary-Treasurer*.

CITY OF WASHINGTON.

The meeting of the City of Washington Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held March 15, 1937, in the assembly room of the AMERICAN INSTITUTE OF PHARMACY.

President Briggs introduced three new members, Mr. Bell, Dr. Rosen and Mr. Sock.

Vote on the proposed amendment to the By-Laws, changing the date of the meeting from the second to the third Monday of the month, was called for, duly seconded and carried.

The president announced that Mr. Warren was unavoidably absent and that he would present his paper at a later meeting.

The first speaker of the evening was Dr. S. L. Hilton, former president of the A. PH. A., and Chairman of the Council. He read a paper entitled "Some Features of Pharmaceutical Recipe Book, II." In giving the history of the book, it was stated "The idea of such a book was conceived by Dr. Henry P. Hynson of Baltimore, in 1909, when he presented the proposal to the Council of the ASSOCIATION." Other portions are given in the paper, which follows this report.

After the reading of the paper, Dr. Hilton exhibited preparations manufactured in his Pharmacy. Among others, these included: Ampuls of Iron Cacodylate, Indigo Carmine, Silver Nitrate, Sodium Bicarbonate, Compound Iodine Paint, Castellani's Lotion, Whitfield's Ointment with Thymol.

In the general discussion, Chief Pharmacist Swann, U. S. Navy, informed the members that in the Navy, the Recipe Book is found in every laboratory and in most of the larger ships.

President Briggs introduced as the next speaker of the evening, Dr. Frank A. Delgado, former first vice-president of the A. PH. A. and Chief of the Medicinal and Toilet Preparation Section, Chemical Division of the Department of Commerce. He read a paper entitled "Pharmacy's Need for Facts." He stated, "One might truthfully say that the future economic progress of Pharmacy in its march forward is going to be largely dependent upon the facts, figures and statistics at its command."

Mr. Delgado attributed the enactment of the Robinson-Patman bill, State Fair Trade legislation and other similar laws to facts, figures and statistics that were made available, and also

cited that the defeat of the frequently introduced Capper-Kelly bill was due to its lack of any supporting and convincing facts.

The speaker gave some enlightening figures and facts such as:

"250,000,000 physicians' prescriptions being compounded annually at a cost of $209,000,000; one store to 2000 population; death rate of 1000 population, 11.9; number of drug stores in 1935, 56,697; in 1933, 58,407 and in 1929, 58,258; sales in 1935 for the 56,519 drug stores amounted to $1,226,491,000, an increase of 15.3% over 1933, but $464,000,000 under the peak of 1929. The number of drug store employees in 1935 was 158,379, an increase of 7.3% over 1933. Average salary per employee (full and part time) in 1935 was $919; in 1933, $985 and in 1929 was $1260. The salaries in drug stores are lower than of apparel stores; slightly higher than of food stores. There were 560 drug store failures in 1935. The number of chain drug stores in 1935 was 3744 units, a loss of 16 units compared with 1933, but a gain of 231 units when compared with 1929. The number of independent drug stores in 1935 was 52,855; 53,341, in 1933, a decrease of 486 units.

"Study of sales figures shows that while chain drug stores constitute only 6.6% of total drug stores, they do 28.8% of the business, an increase over 1933 of approximately 3.7%. Independent drug stores lost ground, having done 81.2% of total retail drug business in 1929, 74% in 1933 and 71.1% in 1935."

Speaking on the subject of salaries paid in drug stores, Mr. Delgado said, "It seems to me that the subject of hours and remuneration in Pharmacy is deserving of more attention on the part of the profession and trade. Long hours have been a part of drug store employees' lot from time immemorial; long hours, hard work and not much to show for it."

"It is doubtful if a study of resolutions passed annually at 48 state pharmaceutical association meetings would disclose any resolutions toward the improvements of the welfare of the registered pharmacists and other retail drug store employees. All indications, however, seem to point to the necessity of an attempt to correct the hour and pay situation in the retail drug industry before forces outside of Pharmacy will take a hand."

In his conclusion the speaker stated: "No doubt some very interesting and, in my opinion, important conclusions could be drawn from the aforementioned figures, but they are by no means complete and until I have the opportunity to correlate such facts and figures as the relationship and bearing that the growth of chain drug stores may have to the decrease in number of all drugs—the ratio of drug chains, sales to independents, drug store sales, and study such factors as density of population, home ownership, persons gainfully occupied, climatic conditions, student enrollments, number of graduates, number successfully passing State Board examinations—personally I refrain from drawing any conclusions The reader is, of course, at liberty to study the foregoing figures and draw any conclusions he may see fit."

After the reading of his paper, Dr. Delgado read a report received from Australia where a campaign was waged successfully by pharmacists, prohibiting the introduction of chain drug stores in that country. A general discussion followed.

Under New Business, A. C. Taylor moved that the president appoint five members as a Committee to be known as the Program Committee—duly seconded and carried.

President Briggs gave a tentative program for the April meeting.

V. B. NORELLI, *Secretary.*

THE A. PH. A. RECIPE BOOK.

BY S. L. HILTON.

The idea of a Recipe Book was conceived by Dr. Henry P. Hynson, of Baltimore, in 1909, when he presented his ideas to the Council of the ASSOCIATION. His proposition with communications from Leo Eliel and Otto Raubenheimer on the subject were referred to the Committee on Standards for consideration and report at the Los Angeles meeting. At that meeting the Committee reported and recommended that the Committee on Standards devote its early attention to the compilation of a list of useful formulas in general use, carefully check them and make them uniform so that no matter where the preparations were obtained they would be uniform and of greater value.

In 1910, the Committee on Nonofficial Standards reported that it was not expedient at that time to complete the Recipe Book as its efforts should be devoted to establishing correct standards for the National Formulary IV, which had been made one of the standards for drugs under the Pure Food and Drugs Act of 1906.

It was then suggested by Otto Raubenheimer that a special committee be appointed to complete the obtaining of formulas for the Recipe Book and that they be properly classified and standardized; this suggestion was approved and a committee of five was appointed which, in the following year, was increased to 25 and has been so continued up to the present time.

Requests were sent broadcast for formulas in common use in this country and before long there were some fifteen hundred formulas collected, these were discussed and tried out by members of the Committee and necessary corrections made where necessary to obtain satisfactory preparations and greater uniformity, a condition much desired as many preparations differed according to the section of the country they came from.

Some formulas were deleted as they had outlived their usefulness, new formulas were tried out and admitted by vote of the Committee and the complete manuscript edited by Professor Ivor Griffith; the book was then published by the AMERICAN PHARMACEUTICAL ASSOCIATION. The sale of this first edition was very gratifying and it soon became necessary to publish a second edition as the first edition was completely exhausted. This was available in the fall of 1936.

After publication, the Committee was continued with some changes in personnel, and work was soon started for the next revision, a number of sub-committees were appointed and each committee had its work mapped out. Let me say they worked in perfect accord and all formulas were thoroughly tested and considered and reported to the full Committee for approval or rejection so that the Recipe Book II is far in advance of the first edition and is a most valuable and helpful book for the pharmacist's library.

All admissions were by a two-thirds vote of the full Committee and the book contains only formulas frequently called for and that can be compounded by the pharmacist.

No responsibility whatever is assumed for the therapeutic value of the formulas or the doses; the doses given are average doses and the formulas contained therein are only those commonly used in this country.

The Recipe Book does not supply imitations of proprietary or trade-marked articles and institution and hospital formulas are included by permission.

The Food and Drug Administration, the Council on Dental Therapeutics, The American Veterinary Medical Association and others have been very helpful and have submitted many formulas. They have offered many valuable suggestions, especially the Food and Drug Administration.

The Book contains the following general subjects: Pharmaceutical Formulas, Hospital Formulas, Dental Formulas, Chiropodists' Formulas, Veterinary Formulas, Laboratory Reagents, Photographic Formulas, Flavoring Formulas, Cosmetic Formulas, Vehicles, Technical and Miscellaneous Formulas, Agricultural Formulas, Industrial Formulas, Methods for Rendering First Aid, Doses, Schedule of Poisons with Their Antidotes, and a Table of Solubilities. The latter table is most helpful to the pharmacist as it gives the solubility of a large number of substances in various liquids, more complete than any other book of reference: Water at 25° C., 100 Centigrade; Alcohol, Chloroform, Ether, Glycerin, the figures given represent the number of cc. of the solvent in which 1 Gm. of the substance dissolves at 25° C., or the temperature otherwise stated to make a saturated solution in the respective solvent. Volume II contains nearly 2000 formulas.

The formulas, etc., have been arranged alphabetically under each part, the English name being accepted as the official title, synonyms are given; the index is most perfect and comprises over 50 pages—fully cross-indexed and where titles have been changed both the old and new titles are given.

No pharmacy is complete without a copy of the Recipe Book II as it contains a wealth of information that can be made a money maker and is well adapted to the manufacturing facilities of the average pharmacy.

ASSOCIATION BUSINESS

AD INTERIM BUSINESS OF THE COUNCIL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, 1936–1937.

Office of the Secretary, 2215 Constitution Avenue, Washington, D. C.

LETTER NO. 10.

March 18, 1937.

To the Members of the Council:

79. Election of Members. Motion No. 36 (Council Letter No. 9, page 269) has been carried and applicants for membership numbered 153 to 209, inclusive, are declared elected.

80. Use of Text of N. F. VI. Motion No. 37 (Council Letter No. 9, page 269) has been carried and Dr. Hatcher has been so advised.

The following communication has been received from Chairman DuMez of the Committee on Publications:

> "I have gone over the sample pages of the manuscript of Dr. F. R. Davison for a text book on pharmacology and recommend that permission be granted him to use portions of the text of the N. F. VI for comment therein..."

(*Motion No. 39*) It is moved by DuMez that Dr. F. R. Davison be granted permission to use portions of the text of the N. F. VI in his book entitled "A Textbook of Pharmacology and Therapeutics, Including Prescription Writing, Materia Medica and Toxicology," with the customary acknowledgment and at the usual charge of $5.00.

81. Committee on Recipe Book. Motion No. 38 (Council Letter No. 9, page 269) has been carried and Messrs. George A. Moulton, Charles E. McCormick and M. G. de Navarre are elected members of this Committee.

82. Applicants for Membership. The following applications, properly endorsed and accompanied with the first year's dues, have been received:

No. 210, William O. Votteler, 1582 Bardstown Rd., Louisville, Ky.; No. 211, Charles H. Tye, Harlan, Ky.; No. 212, Frank J. Schneitzer, Jr., 2567 Bank St., Louisville, Ky.; No. 213, C. W. Krause, 10th & Madison, Covington, Ky.; No. 214, Willard G. Codey, 10th & Madison, Covington, Ky.; No. 215, James A. Simmons, Greensburg, Ky.; No. 216, John L. Cornett, 206 E. Main St., Richmond, Ky.; No. 217, Leo J. Wagner, 3035 So. 4th St., Louisville, Ky.; No. 218, Nathan H. Kaplin, 1049 18th St., Louisville, Ky.; No. 219, Charles H. Howard, Main St., Harlan, Ky.; No. 220, E. C. Sutphin, Box 787, Chapel Hill, N. C.; No. 221, S. A. Bobroff, 307 McCauley St., Chapel Hill, N. C.; No. 222, C. O. Oates, Jr., 410 Ruffin Dorm., Chapel Hill, N. C.; No. 223, John David Smith, 202 W. Rosemary St., Chapel Hill, N. C.; No. 224, Jesse W. Tyson, 202 W. Rosemary St., Chapel Hill, N. C.; No. 225, John F. Rhem, 101 Old West, Chapel Hill, N. C.; No. 226, O. T. Berch, 2111 W. North Ave., Milwaukee, Wis.; No. 227, Ray Miess, 1800 No. Farwell Ave., Milwaukee, Wis.; No. 228, Rudolph L. Yanda, Jr., 57 Crafton Ave., Crafton, Pa.; No. 229, Ralph G. LeMoon, 531 Suisman St., Pittsburgh, Pa.; No. 230, Joseph Peter Resnick, 311 Halkett St., Pittsburgh, Pa.; No. 231, Chester Wm. Krause, 625 Hastings St., Pittsburgh, Pa.; No. 232, Wilbur Grove, 1039 Flemington St., Pittsburgh, Pa.; No. 233, Margaret E. Wade, 7919 Tacoma St., Pittsburgh, Pa.; No. 234, John Wm. Holroyd, 409 Monongahela Ave., Otto, McKeesport, Pa.; No. 235, Salvatore M. Fortino, 511 Main St., Sharpsburg, Pa.; No. 236, Eugene Garretson Smouse, 736 Franklin Ave., Wilkinsburg, Pa.; No. 237, Jane R. Carnahan, 545 Mullberry St., East Liverpool, Ohio; No. 238, Charles F. Brand, 39 Walnut Ave., Wheeling, W. Va.; No. 239, Roderick Walters, 405 Ruxton St., Pittsburgh, Pa.; No. 240, Ralph Wm. Kemerer, Main St., Boston, Pa.; No. 241, Betty J. Haeckler, 373 South Winebiddle St., Pittsburgh, Pa.; No. 242, Robert C. Kealey, 117 N. 5th St., Jeannette, Pa.; No. 243, Robert L. Peel, 548 Spruce Ave., Sharon, Pa.; No. 244, Harry H. Vandervort, Jr., 3306 Dawson St., Pittsburgh, Pa.; No. 245, Ewing Garofalo, 1119 Bluff St., Pittsburgh, Pa.; No. 246, Sidney L. Gondelman, 3366 Webster Ave., Pittsburgh, Pa.; No. 247, Frank J. Chodzinski, 3055 Brereton Ave., Pitts-

burgh, Pa.; No. 248, John Raffensperger Rouzer, 610 26th St., Altoona, Pa.; No. 249, John H. Nosidlak, 401 Maline St., Pittsburgh, Pa.; No. 250, Charles R. Pearce, Good St., Jeannette, Pa.; No. 251, George E. Smith, 1119 Bluff St., Pittsburgh, Pa.; No. 252, Robert E. Williams, 1012 Broadway, East McKeesport, Pa.; No. 253, Timothy A. Lucum, 1411 Page St., N. S., Pittsburgh, Pa.; No. 254, Joseph Kozloski, 605 E. North Ave., Pittsburgh, Pa.; No. 255, Peter John Silvester, 1410 Page St., Pittsburgh, Pa.; No. 256, Charles A. Britcher, Jr., 1024 LaClair St., Pittsburgh, Pa.; No. 257, Walter H. MacWilliams, Naval Medical School, Washington, D. C.; No. 258, C. P. Dean, 1610 N. Taylor St., Arlington, Va.; No. 259, John S. Malcolm, University Hospital, Ann Arbor, Mich.; No. 260, Francis E. Wessinger, University Hospital, Ann Arbor, Mich.; No. 261, Lawrence G. Mann, University Hospital, Ann Arbor, Mich.; No. 262, Don E. Francke, University Hospital, Ann Arbor, Mich.; No. 263, James R. Thayer, 4588 Parkview Pl., St. Louis, Mo.; No. 264, Thomas D. James, 3972 a Utah St., St. Louis, Mo.; No. 265, Lorene M. Massagli, 136 Leland Ave., San Francisco, Calif.; No. 266, Lenita S. Thomas, P. O. Box 604, Hollister, Calif.; No. 267, Gallio Joseph Marzano, Pedro Miguel, Canal Zone; No. 268, Harry N. Trotter, U. S. Naval Hospital, Brooklyn, N. Y.; No. 269, John Ray Dakin, U. S. Naval Hospital, Brooklyn, N. Y.; No. 270, Manuel Horne do Munoz, Munoz Rivera No. 5, Guayanilla, P. R.; No. 271, Hugo L. Menke, 384 Post St., San Francisco, Calif.; No. 272, Edwin Hesse, Jr., 2679 Atlantic Ave., Brooklyn, N. Y.; No. 273, I. Sydney Wolfe, 2487 Bloor St., W., Toronto, Ont., Canada; No. 274, Leander James Eckels, 207 N. Front St., Steelton, Pa.; No. 275, Howard Lee Baker, 4015 Plainville Rd., Cincinnati, Ohio; No. 276, Raymond Watson, 4606 19th St., N., Arlington, Va.; No. 277, C. S. Stonebraker, 2156 Noble Rd., E. Cleveland, Ohio; No. 278, Henry Kot, 6646 N. Clark St., Chicago, Ill.; No. 279, Edward J. Breck, 31 Elm St., Springfield, Mass.; No. 280, Earl Pitcock, Tavern Hotel, Oak Creek, Colo.; No. 281, Louis Manna, 2016 Daly Ave., New York, N. Y.; No. 282, A. J. Shimon, Pocohontas, Iowa; No. 283, Herbert Marshall Cobe, Maplewold Farm, Forest Grove, Pa.; No. 284, Joseph C. Steiminger, 276 Jefferson Drive, Mt. Lebanon, Pittsburgh, Pa.; No. 285, John Claggett Jones, 1121 State Office Bldg., Richmond, Va.; No. 286, Lester E. Bonnin, 2446 N. 45th St., Milwaukee, Wis.; No. 287, J. B. Moore, 613 S. First St., Louisville, Ky.; No. 288, Edmund Edward Goodmaster, 14 Gilbert Ave., New Haven, Conn.; No. 289, Joseph Senelnick, 1580 Bloor St., W., Toronto, Ont., Canada; No. 290, Walter Clayton Spain, 5904 Nottingham Rd., Detroit, Mich.; No. 291, Samuel Rothenberg, 1143 Blue Hill Ave., Dorchester, Mass.; No. 292, Joseph T. Cooley, Jr., A. T. O. House, Gainesville, Fla.; No. 293, Kenneth L. Kelly, Colorimetry Section, Bureau of Standards, Washington, D. C.; No. 294, Wilton C. Harden, 9 Melvin Ave., Catonsville, Md.

(*Motion No. 40*) Vote on applications for membership in the AMERICAN PHARMACEUTICAL ASSOCIATION.

83. Time and Headquarters for the 1937 Meeting. Dr. Hugo H. Schaefer, Local Secretary, has recommended on behalf of the Local Committee on Arrangements that the week of August 16th be approved as the time, and the Hotel Pennsylvania as the headquarters for the 1937 meeting. President Beal and Secretary Kelly recently conferred with Dr. Schaefer in New York about the arrangements for the meeting and concur in this recommendation.

(*Motion No. 41*) It is moved by Kelly that the week of August 16th and the Pennsylvania Hotel be approved as the time and headquarters for the 1937 meeting. A vote on this motion will be called for in about one week.

E. F. KELLY, *Secretary.*

March 24, 1937.

To the Members of the Council:

We regret to announce the death of Honorary President Willis G. Gregory, which occurred at Buffalo, N. Y., on Saturday, March 20th.

The ASSOCIATION was officially represented at the funeral exercises.

E. F. KELLY, *Secretary.*

LETTER NO. 11.

April 1, 1937.

To the Members of the Council:

84. Use of Text of N. F. VI. Motion No. 39 (Council Letter No. 10, preceding) has been carried and Dr. Davison has been so advised.

85. Election of Members. Motion No. 40 (Council Letter No. 10, preceding) has been carried and applicants for membership numbered 210 to 294, inclusive, are declared elected.

86. Time and Headquarters for 1937. As no comment has been received, a vote is called for on Motion No. 41 (Council Letter No. 10, preceding).

87. Report of the Auditor. Mr. W. A. Johnson, Certified Public Accountant, has submitted the following report:

"I have made an examination of the books and accounts of the AMERICAN PHARMACEUTICAL ASSOCIATION and of your report, as Treasurer, for the calendar year 1936, and I hereby certify that the total cash and securities on hand at December 31, 1936, amounting to $216,538.37, is correctly stated.

"All cash receipts have been traced to deposits in banks to the credit of the respective funds for which received, and all disbursements have been found evidenced by properly authorized voucher checks.

"Cash on deposit has been reconciled with statements submitted by the banks as of the close of the year or verified by comparison with certificates of deposit.

"Investment securities, having a face or par value of $138,100.00, have been verified by examination of the bonds or certificates. No changes were made in the investment portfolio during the year.

"Interest accruing on registered bonds and on coupons attached to other bonds have been properly accounted for on your report and have been deposited to the credit of the proper accounts in the depositories of the ASSOCIATION, except for the following coupons which are in default:

Headquarters Building Fund
$200 Chicago, Milwaukee & St. Paul R. R. 5% bonds,
coupons due February 1, 1936 and August 1, 1936.

Life Membership Fund
$100 City of Detroit, Mich. 4% bonds,
coupons due Nov. 15, 1932, May 15, 1933 and Nov. 15, 1936.

"In each case of default of interest the unpaid coupon has been attached to the bond and returned to the safe deposit vault of the ASSOCIATION.

"Records maintained by the Secretary of the ASSOCIATION have been examined and transfer of funds from his account to that of the Treasurer have been verified and found to be correctly stated."

The Treasurer's Report for 1936, which includes the following summary of accounts will be published in full later:

COMPARISON OF FUNDS.

Current Fund.

	Dec. 31, 1935.	Dec. 31, 1936.
Deposit in Merchants & Newark Trust Co.	$ 765.38	$ 30,793.43
Deposit in Boston Penny Savings Bank	419.88	430.43
Deposit in Baltimore Trust Company	1,638.61	1,536.20
Total Current Funds	2,823.87	32,760.06

Permanent Funds.

Endowment Fund	17,273.60	17,773.14
Centennial Fund	6,098.77	6,242.99
Ebert Legacy Fund	8,916.38	9,227.63

Ebert Prize Fund	1,076.63	1,054.67
Life Membership Fund	33,828.53	34,133.31
Endowed Membership Fund	129.05	129.05
Research Fund	68,138.54	69,040.98
Headquarters Building Fund	552,907.73	560,946.99
Total Permanent Funds	688,369.23	698,548.76
Trust Funds.		
F. B. Kilmer Fund	.....	3,000.00
Wm. Procter, Jr., Monument Fund	18,487.80	19,073.28
Jos. P. Remington Honor Medal Fund	1,331.22	1,343.64
Total Trust Funds	19,819.02	23,416.92
Summary of Funds.		
Current Fund	2,823.87	32,760.06
Permanent Fund	688,369.23	698,548.76
Trust Funds	19,819.02	23,416.92
Total Funds	$711,012.12	$754,725.74

SUMMARY OF ASSETS AND TRUST FUNDS.

	Dec. 30, 1933.	Dec. 30, 1934.	Dec. 31, 1935.	Dec. 31, 1936.
Current Fund	$ 6,284.72	$ 4,196.01	$ 2,823.87	$ 32,760.06
Permanent Funds	625,569.92	680,507.27	688,369.23	698,548.76
Total Assets	631,854.64	684,703.28	691,193.10	731,308.82
Trust Funds	18,580.11	19,214.15	19,819.02	23,416.92
	$650,434.75	$703,917.43	$711,012.12	$754,725.74

SUMMARY OF DEPOSITS, SECURITIES AND PROPERTY.

Deposit in Baltimore National Bank	$ 18,713.32	
Deposit in Merchants & Newark Trust Co	30,793.43	
Deposit in Boston Penny Savings Bank	443.95	
Deposit in Baltimore Trust Co	5,928.05	
Deposit in Maryland Trust Co	22,559.62	
Securities in Baltimore National Bank	138,100.00	
Property in Washington, D. C	538,187.37	
Total Deposits, Securities and Property, December 31, 1936		$754,725.74

88. Applicants for Membership. The following applications, properly endorsed and accompanied with the first year's dues, have been received:

No. 295, Andrew L. Croal, 500 So. Third St., Las Vegas, Nevada; No. 296, Darrell Lee Janzen, Box 2, Shafter, Calif.; No. 297, Elvin Schmidt, 406 No. Maclay, San Fernando, Calif.; No. 298, Jerome C. Bryant, Jr., 405 California St., El Monte, Calif.; No. 299, Eiko Matsui, 532 Silver St., Elko, Nevada; No. 300, George M. Halstead, 101 N. Bushnell, Alhambra, Calif.; No. 301, Thomas Everette Mayo, 2009 Fairburn Ave., Los Angeles, Calif.; No. 302, Abraham Morton Gordon, 1815 E. 2nd St., Los Angeles, Calif.; No. 303, Cecil Winston Rea, 911 W. 35th St., Los Angeles, Calif.; No. 304, Samuel James Velis, 1146 So. Lorena St., Los Angeles, Calif.; No. 305, Dario John Balzano, 2606 Huron St., Los Angeles, Calif.; No. 306, Florence Hideko Tanase, 847 Exposition Blvd., Los Angeles, Calif.; No. 307, Sister M. Elizabeth, 716 Yale St., Los Angeles, Calif.; No. 308, Edward John Bradel, 316 Thorn St., Sewickley, Penna.; No. 309,

Leonard Bernard Klein, 14 Whiteside Rd., Pittsburgh, Pa.; No. 310, George Brunner, 522 Dippold Ave., Baden, Pa.; No. 311, P. Joseph Augustine, Fourth St., Sutersville, Pa.; No. 312, Edward N. Koch, Jr., 5631 Woodmont St., Pittsburgh, Pa.; No. 313, Edward A. Sport, 12 Magee St., Cambridge, Mass.; No. 314, Paul B. Elder, 805 E. Mulberry St., Bryan, Ohio; No. 315, George W. Drain, 916 Parrish St., Philadelphia, Pa.; No. 316, Eleanor Kairis, Sinai Hospital, Baltimore, Md.; No. 317, Jacob Louis Cohen, 531 N. Beatty St., Pittsburgh, Pa.

(*Motion No. 42*) Vote on applications for membership in the AMERICAN PHARMACEUTICAL ASSOCIATION.

E. F. KELLY, *Secretary.*

ACTION ON PROPOSED AMENDMENTS TO THE BY-LAWS.

SUBSEQUENT to the annual meeting of the ASSOCIATION in Portland, Oregon, in 1935 President Costello appointed a committee to study the *Constitution and By-Laws* in accordance with a resolution which grew out of certain recommendations made by President Fischelis at that meeting, see August 1935 issue of the JOURNAL, page 655.

The Committee was requested to apprise the membership in advance of the Dallas meeting, of the changes proposed, and the preliminary report of the Committee was published in the July 1936 issue of the JOURNAL, page 649.

The majority and minority reports of the Committee were submitted during the First General Session of the meeting at Dallas, and were considered and acted on in part at the Second General Session, as reported in the October 1936 issue of the JOURNAL, pages 892 and 908, respectively. Action on several proposed amendments was postponed until the next annual meeting and the purpose of this statement is to direct the attention of the membership to these proposed amendments to the By-Laws, to the discussion of them and to the fact that they will come up for action at the New York meeting in August.

ARRANGEMENTS FOR ANNUAL MEETING OF THE AMERICAN PHARMACEUTICAL ASSOCIATION.*

The Annual Meeting of the AMERICAN PHARMACEUTICAL ASSOCIATION and its affiliated groups will be held in New York City during the week of August 16, 1937. The Local Committee in coöperation with Local Secretary Hugo H. Schaefer, has selected the Hotel Pennsylvania as Convention Headquarters. This hotel is the largest of the Statler group, with 2200 rooms and 2200 baths. It is connected by underground passage with the Pennsylvania Railroad station, the Hudson Tubes and the city subways. Garage facilities also are very convenient. *The rates begin at $3.50 single and $5.00 double.* All rooms are with bath, radio and circulating ice water. There are five hotel restaurants—from cafeteria to night club—with reasonable prices. It is significant that the first convention ever held in this Hotel was that of our ASSOCIATION—just eighteen years ago. The Hotel management has not forgotten this fact and intends to surpass itself in making our 1937 meeting something in the nature of a celebration.

With the recent general reduction in transportation rates, all special convention rates have been discontinued except where a number of persons may travel from the same point as a party. Inquiry about transportation should be made of the local agent.

The Local Committee is busy arranging an elaborate and interesting entertainment program, including a boat ride to Bear Mountain, a night-club evening, a banquet with lavish vaudeville entertainment, besides the usual sight-seeing trips, visits to industrial plants, Radio City and a Trans-Atlantic liner.

---

* From Bulletin No. 14, A. PH. A.

The various officers, including those of the sections and affiliated organizations report that an unusually large number of interesting papers and reports will be presented at the meetings, and speakers of prominence will address the various sessions.

The banquet hall, ball room and all meeting rooms will be air cooled. Everything points to a record meeting—in attendance, in interest and in entertainment. Reservations should therefore be made as early as possible.

SYRUPS TO HIDE OBJECTIONABLE TASTES.

Syrups of Cacao, Raspberry and Eriodictyon were shown to be the "all purpose" flavoring agents of choice in a series of tests conducted over a period of three years at the University of Minnesota Medical School Department of Pharmacology, reported by Dr. Harold N. Wright, in the *Journal of the American Medical Association*.

Syrups of Cherry, Sarsaparilla, Orange, Citric Acid and Cinnamon were all grouped closely together, as second-grade flavoring agents, and Syrups of Wild Cherry, Licorice and Aromatic Elixir were found to be the least efficient flavoring and disguising agents.

Dr. Wright presented the following table to indicate the percentage scores given these various syrups:

Flavoring Agent.	Score.
Syrup of Cocoa, N. F. V	71
Syrup of Prepared Cacao, N. F. VI	67
Syrup of Raspberry, N. F. VI	68
Compound Syrup of Eriodictyon	59
Syrup of Cherry, N. F. VI	52
Compound Syrup of Sarsaparilla	48
Syrup of Orange	48
Syrup of Citric Acid	47
Syrup of Cinnamon	46
Syrup of Wild Cherry	35
Elixir of Licorice	32
Aromatic Elixir	27

The percentage scores given here represent a composite derived from tests made to discover which materials were preferred for flavoring alone, which were more efficient in disguising effectively bitter taste, ammonium chloride (saline taste) and tincture of digitalis. Groups of students were asked to taste four flavors at a time, or four combinations of the various drugs with flavors, and to indicate their preferences.

Three points were given for first choice, two for second choice, one for third and no credit for fourth choice. The results were expressed as a percentage of perfect first choice.

Dr. Wright suggests that a score of 75 per cent or more was considered highly effective, from 60 to 65 per cent indicates a second-grade flavoring agent, from 35 to 50 per cent, third grade, and less than 35 per cent as practically worthless.

During the four-year period, statistical studies showed the tests to be fairly reliable among the several groups tested.

It was found that the flavoring agents were not equally effective for the three types of bad taste desired to be camouflaged. For testing the efficiency of the syrups to disguise the bitter taste of alkaloids, 0.1 per cent quinine bisulfate is added to the various flavoring agents. According to Dr. Wright, this produced a bitter taste sufficiently intense so that it was not completely masked by any of the flavoring agents, and corresponded to a greater degree of bitterness than is produced by a solution of codeine sulfate containing 30 mg. ($^1/_2$ grain) to the teaspoonful.

For the saline test, ammonium chloride was added until a concentration of 8 per cent was reached, corresponding to a preparation containing 0.4 grams (6 grains) of ammonium chloride per teaspoonful.

For the test on digitalis, the tincture of digitalis was added until a concentration of 10 per cent was reached, corresponding to approximately 0.5 cc. of tincture of digitalis to each teaspoonful.

The following composite table taken from Dr. Wright's work indicates the efficiency of the various flavoring materials for the various types of materials tested. Column 1 shows the percentage preference for the flavor taken by itself. Column 2—efficiency in disguising bitter taste, Column 3, efficiency in disguising ammonium chloride, and Column 4 in disguising tincture of digitalis.

Flavoring Agents.	1.	2.	3.	4.
Syrup of Cocoa, N. F. V	91	81	41	..
Syrup of Prepared Cacao, N. F. VI	88	67	34	77
Syrup of Raspberry, N. F. VI	71	77	40	83
Syrup of Orange	53	21	61	57
Syrup of Cherry, N. F. VI	51	48	47	60
Cpd. Syr. of Sarsaparilla	48	39	58	..
Syr. of Citric Acid	46	35	50	60
Aromatic Syrup Eriodictyon	35	73	54	73
Elixir of Licorice	33	27	35	..
Syrup of Cinnamon	32	41	64	..
Syrup of Wild Cherry	29	14	41	54
Aromatic Elixir	27	27	23	32
Syrup of Licorice	26	12	11	..
Tincture of Vanillin 20% in Syrup				59

Iso-alcoholic elixirs and 10 per cent tinctures of vanillin have values below 25 which may be used for disguising digitalis.—Through *Drug Topics*.

THE RELATIVE IN VITRO ACTIVITY OF CERTAIN ANTISEPTICS IN AQUEOUS SOLUTION.

A valuable report of work from the Mallory Institute of Pathology, Boston City Hospital, is published in the January 23, 1937, *Journal A. M. A.* by Robert H. Nye, M.D., Boston. The list of antiseptics employed is given in the following; this number of the *Journal* should be noted by pharmacists for the prescription department, and by laboratory workers.

LIST OF ANTISEPTICS EMPLOYED.

All proprietary solutions were purchased, when possible, in the open market. The non-proprietary solutions were prepared in this laboratory. In each instance the usable strength is given. The dilutions noted in the results refer to dilutions of the respective usable dilutions.

SOLUTIONS CONTAINING IODINE.

1. Compound solution of iodine, U. S. P. Usable strength undiluted. Iodine content 5 per cent (1:20) when titrated with a standardized tenth-normal sodium thiosulfate solution.
2. Iodine solution (nonalcoholic). Usable strength undiluted. Iodine content 0.78 per cent (1:128), titrated as above. Submitted by Amend Laboratories, Inc., New York.
3. Compound solution of iodine, U. S. P., diluted 1:6.4. Usable strength undiluted. Iodine content 0.78 per cent (1:128), titrated as above.
4. Compound solution of iodine, U. S. P., diluted 1:27.8. Usable strength undiluted. Iodine content 0.18 per cent (1:555), titrated as above.

SOLUTIONS CONTAINING MERCURY.

1. Metaphen (1:500). Usable strength undiluted. Manufactured by Dermatological Research Laboratories, Philadelphia.
2. Merthiolate (1:1000). Usable strength undiluted. Manufactured by Eli Lilly & Co., Indianapolis.
3. Mercurochrome (1:50). Usable strength undiluted. Salt manufactured by Hynson, Westcott & Dunning, Inc., Baltimore. Solution prepared in the dispensary, Boston City Hospital.

4. Mercuric oxycyanide ("containing mercury cyanide"—Merck) (1:4000). Usable strength undiluted.

5. Mercury bichloride (Vaidhulis-Arnold modification, aqueous) (1:1000). Usable strength undiluted.

6. Merphenyl nitrate (1:1500). Usable strength undiluted. Obtained through the courtesy of Hamilton Laboratories, Inc., Hamilton, Ohio.

7. Merphenyl borate (1:500). Usable strength undiluted. Obtained through the courtesy of Hamilton Laboratories, Inc., Hamilton, Ohio.

SOLUTIONS CONTAINING CHLORINE.

1. Zonite. Usable strength 1:2. Available chlorine content (diluted) 0.53 per cent (1:190), titrated, after conversion to iodine, with a standardized tenth-normal sodium thisosulfate solution. Manufactured by Zonite Products Corporation, New Brunswick, N. J.

2. Apco No. 25, diluted 1:8.3. Usable strength undiluted. Available chlorine content 0.39 per cent (1:260), titrated as above. Dilution made in the dispensary, Boston City Hospital. Manufactured by Ampere Products Company, West Orange, N. J.

MISCELLANEOUS SOLUTIONS.

1. Hexylresorcinol (1:1000). Usable strength undiluted. Manufactured by Sharp & Dohme, Baltimore.

2. Listerine (25 per cent alcohol). Usable strength undiluted. Manufactured by Lambert Pharmacal Company, St. Louis.

3. Pepsodent (25 per cent alcohol). Usable strength undiluted. Manufactured by Pepsodent Company, Chicago.

All these antiseptics were tested simultaneously for (1) bactericidal activity, (2) bactericidal activity in mixtures containing 50 per cent horse serum, (3) diffusibility and (4) toxicity. In addition, figures representing unit costs were obtained. The methods employed and the results obtained are reported in the article.

COMPARISON OF SALES OF CHAIN STORES IN 1929 AND 1935.

Liberty is taken in reprinting the comparison of sales herewith from the current issue of the *Druggists Circular*, as prepared by Paul C. Olsen for that publication.

	Per Cent of Drug Store Sales Made in Chain Drug Stores.			Per Cent of Drug Store Sales Made in Chain Drug Stores.	
	1935.	1929.		1935.	1929.
Washington	57.4	60.1	Boston	29.8	30.2
Chicago	48.1	35.2	New York	26.8	25.4
Cleveland	46.4	34.6	Buffalo	26.3	16.5
Pittsburgh	44.6	40.1	Philadelphia	24.7	21.3
Detroit	44.2	33.6	Average for 14 largest cities	37.2	30.0
San Francisco	38.8	20.0	Average for U. S. outside 14 largest cities	21.8	14.4
Baltimore	38.5	28.7	Average for entire U. S.	25.7	18.5
St. Louis	38.4	26.2			
Milwaukee	38.3	30.3			
Los Angeles	33.8	30.0			

VALUE OF "PATENT" AND "PROPRIETARY MEDICINES."

The aggregate value of druggists' preparations and patent or proprietary medicines made in 1935 amounted to $275,223,159, an increase of 15.2 per cent as compared with $238,823,903 reported for 1933. Manufacturers engaged primarily in the production of these classes of preparations and medicines employed 22,129 wage earners in 1935 and expended $21,978,878 in wages.—From *Standard Remedies*.

WILLARD W. EGGLESTON, AN APPRECIATION.

BY HEBER W. YOUNGKEN.

WILLARD WEBSTER EGGLESTON was born at Pittsfield, Vt., March 28, 1863. He received his early education in the public schools of Rutland, Vt., and later entered Dartmouth College from which he graduated with the degree of B.S. in 1891. After graduation from Dartmouth, he practiced civil engineering at Rutland, Vt., until 1907, when he became interested in botany and entered the employ of the New York Botanical Garden. In 1907 he received a research scholarship at that institution which he held until 1909. From 1908 to 1909 he also served as botanical assistant at the U. S. National Museum. In 1910 he was appointed assistant botanist in the Forest Service and Bureau of Plant Industry at Washington. His initial work there was that of investigating stock poisoning by plants on the National Forest Ranges. He was particularly fitted for this work, having been engaged for 15 years or more in collecting and determining plants of this country. For many years he was active in surveying grazing areas in the western part of the United States and in collecting and listing the species of Cosmos plants found in those areas, specimens of which numbering several thousand having been deposited by him in the U. S. National Herbarium, The New York Botanical Garden and in The Gray Herbarium of Harvard University.

About 15 years ago Mr. Eggleston became actively interested in the geographical distribution of medicinal plants and, in recognition of his work in this field, was in 1927 elected a member of the Committee on Pharmacognosy and Pharmaceutical Botany of the Division of Biology and Agriculture of the National Research Council. He served this committee very faithfully until the end, collecting data in many sections of the United States for its Census on Medicinal Plants.

In 1926 Mr. Eggleston joined the Plant Science Seminar and not only became a regular member attending most of its meetings but participated most helpfully on many of its field trips. His eagerness to share his vast store of information on the plants in regions first visited by most of the Seminar members and his genial personality will be remembered by all who attended the Seminar meetings with him. He was especially interested in the genus *Cratægus* in which group he was a recognized authority. He revised the monograph on *Cratægus* in the last edition of Gray's "Manual of Botany."

Mr. Eggleston was a member of the Botanical Society of America, The Torrey Botanical Club, The Washington Botanical and Biological Societies, The New England Botanical Club, The Appalachian Mountain Club and The Vermont Botanical Club, serving as vice-president of the last from 1912 to 1914. He was a member of the First Congregational Church of Washington, D. C., and Bronx Lodge I. O. O. F. of New York City. He has published a number of articles on early botanists and botanical explorations in the United States among which may be mentioned "The Early Botanists of the Green Mountains, with an Account of C. C. Frost's Visit to Mt. Mansfield and Smuggler's Notch," "Dr. Ezra Brainerd," "Dr. Josiah Whitney Barstow," "Alphonso Wood's Description of Willoughby Lake and Its Flora," and "Charles C. Frost's Trip to Willoughby Mountain."

Mr. Eggleston's chief hobby and interest was in the field of systematic botany. He was very much at home in the field, woodland and swamp, and with his collections, a very keen observer of the features of plants, not given to publishing many of his observations, but always generous in recounting his experiences to others.

For the past several years he suffered frequent illnesses, the last of which followed shortly after returning from a collecting trip in New York and Northern New Jersey for the Committee on Pharmacognosy and Pharmaceutical Botany of the National Research Council. He died at his home in Washington, D. C., on November 25, 1935, and was interred in Rock Hill Cemetery, Foxboro, Mass. He is survived by his widow, Mrs. Alma L. Eggleston.

Dr. Eggleston's passing on is a distinct loss to the Seminar which he loved and to which he gave considerable of his time and energy. His companionship will be sadly missed by our members especially on the field trips where, on many an occasion, he added materially to the enjoyment and profit of the outing.

EDITORIAL NOTES

RESEARCH FOR PROGRESS.

Touching briefly upon the general value of research as something already known to his audience, Dr. A. G. DuMez, dean of the School of Pharmacy of the University of Maryland, outlined certain applications of research, which he believed pharmaceutical manufacturers would find it advisable to undertake and to promote. In this connection he gave some information on the institutions best equipped to carry out research of specific types. He considered in several aspects research in commercial, chemical, pharmacological, pharmaceutical, botanical and clinical lines.

Standardization of unofficial preparations was discussed by Mr. DuMez, who considered this a desirable undertaking, and he told of the plan of the AMERICAN PHARMACEUTICAL ASSOCIATION to revive its work in this connection and establish a laboratory in this field.

Schools of pharmacy are steadily becoming better equipped to serve manufacturers in research, Dr. DuMez said, and he believed that it was logical that this service should be utilized as it promised the best treatment of many problems. He referred his hearers to Dr. Ernest Little, dean of the New Jersey College of Pharmacy, Newark, for particulars and assistance in this connection, Dr. Little being the chairman of the executive committee of the American Association of Colleges of Pharmacy and having made a particular study of research facilities.—From *Oil, Paint and Drug Reporter*.

STERILIZING UTENSILS.

The International Pharmaceutical Federation advises that during the sessions of the International Congress of Pharmacy in Brussels Professor B. Koskowski presented a report on the "Necessity of Sterilizing Medical Utensils."

The conclusion of this report is as follows:

"A pharmacy, as an institution devoted to health, should exercise care not to be a focus of contagion; the installations should be aseptic; the free use of glass on the tables, counters, etc., and the sterilization of the utensils used in the practice of pharmacy should give the impression of an establishment kept in a most cleanly condition. In this manner public confidence is won.

"We should not wait for the inspecting authorities to intervene in these questions and give orders which will impose aseptic conditions in pharmacies. I submit to the consideration of the 12th International Congress of Pharmacy in Brussels my proposal for the adoption by all pharmacies of the sterilization of medical utensils."

The Congress adopted this conclusion unanimously. However, that fact does not give the Bureau of the International Pharmaceutical Federation authority to undertake any further measures. Nevertheless, the Bureau of the International Pharmaceutical Federation asks attention be given to this problem, and it is hoped to have reports.

BLACK WIDOW SPIDERS.

Science of April 16th, in its supplement states that Black Widow Spiders were known to the Aztecs of pre-Columbian Mexico. The Aztecs knew, too, that the spiders were poisonous, yet they were not afraid of them. For they knew another thing, which few present-day white men are willing to believe—that the black widow's bite is rarely fatal, even though it may make the victim uncomfortably ill for several days. Dr. C. H. Curran, of the American Museum of Natural History, has dug up out of old Spanish records the notes about the black widow set down by the scholarly missionary Sahagun, to whose encyclopedic writings about Mexico the modern world owes the larger part of its knowledge of Aztec life. Sahagun estimated the black widow briefly, but correctly: "There are some poisonous spiders in this country, they are black and have a reddish tail. The stings cause great fatigue for three or four days, although they do not kill with their sting." Aztec doctors treated black widow bites with compresses soaked in an alkaline solution, and also gave the patient an alkaline drink. Complete rest for several days was a necessary part of the cure.

PUBLIC HEALTH SERVICE.

It is understood that the National Institute of Health is planning the establishment of a center for Public Health Service research activities at Bethesda, Md., and that the plans for the center are maturing rapidly. The

change brings the opportunity for Dr. George W. McCoy to return to his favorite study of leprosy, with which his name has long been identified as an investigator.

NEW AND NONOFFICIAL REMEDIES.

THE FOLLOWING ADDITIONAL ARTICLES HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO NEW AND NONOFFICIAL REMEDIES. A COPY OF THE RULES ON WHICH THE COUNCIL BASES ITS ACTION WILL BE SENT ON APPLICATION.—PAUL NICHOLAS LEECH, *Secretary*.

ACRIFLAVINE NEUTRAL-CALCO (See New and Nonofficial Remedies, 1936, p. 189).

The following dosage form has been accepted:

Acriflavine Neutral-Calco, Vaginal Capsules, 1/2 grain: Acriflavine neutral-Calco 1/2 grain (0.033 Gm.) in a one-half ounce soluble gelatin capsule containing an excipient the composition of which is sugar of milk, starch and talc.

RINGER'S SOLUTION.—Aqueous solution containing, in 1,000 cc., sodium chloride 7.0 Gm., potassium chloride 0.30 Gm., and calcium chloride 0.25 Gm.

Actions and Uses.—Ringer's Solution is used when chlorides and sodium, potassium and calcium have been diminished. It is indicated in all forms of dehydration but particularly in cases in which loss of gastro-intestinal secretions has resulted from vomiting, diarrheas or fistulas. It is also used in acidosis or alkalosis for improvement of circulation and stimulation of renal activity.

Dosage.—Ringer's Solution is given by all parenteral routes, chiefly subcutaneously and intraperitoneally.

Ringer's Solution in Filtrair Container: Each 100 cc. contains sodium chloride-U. S. P. 0.7 Gm., potassium chloride-U. S. P. 0.03 Gm., and calcium chloride (anhydrous) 0.025 Gm. Marketed in bottles (Filtrair containers) of 500 and 1,000 cc.

Prepared by Hospital Liquids, Inc., Chicago.

Ringer's solution occurs as a clear, colorless solution, possessing a slightly saline taste. The specific gravity is from 1.005 to 1.006 at 25 C. Twenty-five cc. of the solution concentrated to 10 cc. conforms to the U. S. P. XI test for heavy metals; 10 cc. of the solution conforms to the U. S. P. XI test for arsenic.

For limits of potassium, calcium, etc.—see *Journal A. M. A.*, March 6, 1937.

INTERNATIONAL EXCHANGE OF PHARMACISTS.

A proposal for the interchange of pharmacists between various countries of the world has been submitted to pharmaceutical organizations affiliated with the International Pharmaceutical Federation, following a suggestion made by the German Pharmaceutical Society.

The proposed conditions under which exchanges may be arranged are:

(*a*) Duration of exchange period—six months;

(*b*) Pharmacists selected for exchange must not hold appointments in their own country at the time of selection;

(*c*) All costs of voyage and expenses in country to which they proceed are to be paid by pharmacists selected for exchange.

THE SEALING OF GELATIN CAPSULES.

In dispensing small numbers of soft gelatin capsules it is customary to seal the capsules with the aid of a hot spatula or glass rod. This method is not entirely satisfactory, as it is difficult to obtain a neat seal, and one which is reliable in keeping the contents in the capsule. Moreover, it frequently happens that the hot iron or glass discolors the gelatin. To overcome these drawbacks, the following method has been adopted: Steam is generated from a pointed bent glass tubing inserted through a stoppered test-tube. The capsule is held in the steam within the area of dryness. A rapid seal is effected, which is neat, strong and free from any trace of charring. Instead of a glass apparatus, a flat oil-can such as is supplied with cycles and sewing machines, may be used.—By S. J. STARKEY in *The Pharmaceutical Journal*.—Feb. 27, 1937.

PRIMITIVE MEDICINE.

Dr. J. P. Todd, professor at Royal Technical College, Glasgow, recently said: "I have recently been reading some books of extraordinary interest which deal with the medicine men of the native tribes of Africa and the South Sea Islands. It came as a surprise to learn how much these people knew about disease and medicine, even if their knowledge was empirical rather than scientific. During the recent Abyssinian campaign a native soldier was badly wounded by a splinter of a steel shell. An amateur surgeon operated, his instruments being scalpels made of sharpened fresh-water mussel shells fixed on stick. Before operating he plunged them into boiling water to "kill evil." The wounded man was operated on and the splinter removed. Then the wound was treated with an antiseptic made from a local plant, and the wound sewn up with needles and the thread of a tree bark. In ten days the wound had healed. In parts of New Guinea bleeding is stopped by the application of leaves possessing a styptic effect, and home-made ligatures are used.

Some anæsthetics, such as cocaine in the form of coca leaves, were known to primitive people long before they were used in this country. Cinchona, jalap and eucalyptus were all used in the tropics long before their employment here in hospitals."—*Pharmaceutical Journal* (England); March 6th, page 252.

MUNICH PHARMACY MUSEUM.

The German Pharmacists' Association is appealing to its members for contributions for the Museum of Pharmacy in Munich. It demonstrates the use of medicines in the course of the centuries, beginning with the medicinal herbs as employed in 2000 B. C.

DANISH APOTHECARY SHOP—1780–1800.

It is announced in a February 1937 issue, of *Arch. Pharm. og Chemi* that a typical Danish apothecary shop of the period 1780–1800 is to be established at the museum of folk culture at Køpstad, Denmark. The museum is known as "The Old Village" (*Den gamle By*). A brick and timbered house, one of the oldest dated buildings of its type in Denmark, has been assigned to house the project. A committee of apothecaries and professors of pharmacy has been formed to plan the exhibit and to raise the necessary funds. The treasurer is Apothecary Carl Stub of Skanderborg, Denmark. Subscriptions are solicited.—*Courtesy of C. S. Leonard.*

NUMBER OF LICENSES OF JAPANESE PHARMACISTS.

The Japanese Home Department has recently completed an investigation into the number of licenses issued to pharmacists, physicians, dentists. . During the ten years between 1925 and 1935, 13,945 licenses have been issued of which 4231 were re-written and 734 were re-issued. The results show that an average of 1394 pharmacists increased every year during the ten years under review.—*Japanese Retail Pharmacist.*

LIABILITIES ARE LOWER.

BUSINESS CONDITIONS.

A sharp decrease in the number of failures in the manufacturing as well as the retail branch of the drug industry in 1936 as compared with 1935 is shown in a recent report by Dun and Bradstreet. The report shows that for manufacturers of chemicals and drugs there were 61 failures with liabilities of $1,411,000 in 1936 as compared with 87 failures and liabilities of $2,151,000 in 1935.

PERSONAL AND NEWS ITEMS.

Dean Edward Spease, of Western Reserve School of Pharmacy, addressed the City Club of Cleveland, March 20th, on national Food and Drug Legislation, past and present. The Saturday noon talks at the City Club are regularly broadcast, and because of the importance of the subjects discussed and the general competence of the speakers these broadcasts are widely listened to. The talk evoked from the critical audience a warm response, and the gist of Professor Spease's talk was printed in the newspapers.

Our fellow-member, **Professor Charles F. Heebner,** has rendered splendid service to pharmacy in Toronto and throughout Canada. He has also gained recognition Masonically and *Bulletin* 496 is largely devoted to his record. It contains a sketch of his activities in Pharmacy and an appreciation of the Masonic bodies. The sketch of the Dean ends with these words: "A more-or-less imaginary line which separates two neighbor nations has long ago tied them in bonds of friendship, and coöperation in pharmacy is as general between the pharmacists of Canada and the United States as among those of respective countries." He is an alumnus of New York College of Pharmacy. The appreciation evidences the high esteem in which our member is held.

The Masonic meeting of April 14th was known as "Pharmacy Night," at which time Dean Heebner presided and the candidate for degrees was the son of a pharmacist.

MINNESOTA STATE PHARMACEUTICAL ASSOCIATION.

Dean Emeritus Frederick J. Wulling was honored at the fifty-third annual banquet of the Minnesota State Pharmaceutical Association on April 7th. At this time tributes were paid to the retiring dean and the banquet dedicated to him. At this time, also, formal presentation of a memorial plaque was made by President Frederick K. Kustermann of the Alumni Association. President Roy G. Paulson of the Association presided as toastmaster.

Greetings were read from Governor Elmer Benson, John W. Dargavel, Jesse B. Slocumb and Dean C. H. Rogers.

Nearly 900 guests were seated at the table and following the banquet a musical program was rendered.

The bronze tablet measures 15" x 22" and contains the former dean's picture and an inscription paying tribute to him.

CRIME AND SLEEPING POTIONS.

Dean Robert C. Wilson is leading a drive for control of the sale of hypnotics in Georgia. He states: "Jails and penitentiaries are being filled with people, who, under the influence of some one of these hypnotics, have yielded to the suggestion of committing some crime."

South Carolina Pharmaceutical Association will hold its annual convention in Charleston on June 8th and 9th. John Frierson, of Charleston, has been appointed chairman of the committee on arrangement.

TWO PHARMACISTS FOR ARMY CORPS POSTS.

President Roosevelt has appointed two pharmacists to the Medical Administrative Corps of the Army under the act adopted at the last session of Congress. The pharmacists are Glenn Keith Smith, of Lindsay, Calif., and Howard Brim Nelson, of Salt Lake City, Utah, both of whom were made second lieutenants in the regular Army. All Army appointments are made by the President and confirmed by the Senate. Both the pharmacists have been confirmed.

METRIC SYSTEM IN URUGUAY.

A Presidential decree of September 25, 1936, consolidates previous laws requiring the use of the decimal metric system and establishes regulations governing the manufacture, use and control of numerous instruments of measure, according to the Diario Oficial, Montevideo, Uruguay, October 15, 1936. Besides prohibiting the use of all systems of measure other than the metric system, this decree provides for the regulation of scales of all kinds.

PENNSYLVANIA LEGISLATION.

House Bill No. 622 provides for compulsory Health Insurance; in House Committee on Public Health and Sanitation the Legislative Committee expressed opposition to this bill. Senate Bill No. 703 is practically drafted on the Federal Copeland Bill recently passed by the Senate.

House Bill No. 1785 would permit every person registered in Pennsylvania as "Assistant Pharmacist" and who has had fifteen years' experience, to apply for registration as Pharmacist during a thirty-day period following enactment of this bill.

Senate Bill No. 534 would limit the number of drug stores. It restricts the sale of drugs, medicines, etc., in Pennsylvania, unless the person is a Pharmacist, or Assistant Pharmacist. *The Pennsylvania Pharmacist* of March states that the bill is not specific enough on the sale of "Household Drugs."

OBITUARY.

C. O. BIGELOW.

Clarence Otis Bigelow, president of the West Side Savings Bank, Sixth Avenue and Ninth Street, and president and treasurer of C. O. Bigelow, Inc., apothecaries, at 414 Sixth Avenue, died March 28th at St. Luke's Hospital, after three weeks' illness. Mr. Bigelow, who was eighty-five years old, had been active in banking and other business until he became ill.

Mr. Bigelow, who was born in Warwick, R. I., attended schools in Massachusetts before coming to New York, where he studied at the New York College of Pharmacy. Beginning as a clerk, he later became owner of the drug business which bears his name.

In 1888 Mr. Bigelow became a trustee of the West Side Savings Bank, and president twenty-three years later. He served as treasurer of the department of pharmacy of Columbia University and was chairman of the New York State Board of Pharmacy from 1898 to 1918. He was a director of the Fellows Medical Manufacturing Company, a member of the Chamber of Commerce of New York, the Merchants' Association, the Washington Square Association, the Sons of the Revolution, the New England Society, Ye Olde Settlers' Association, the AMERICAN PHARMACEUTICAL ASSOCIATION, the German Apothecary Society, the New York State Pharmaceutical Association and the New York County Pharmaceutical Society.

He was a member of the Union League Club, Salmagundi Club and St. Andrew's Gold Club. Mr. Bigelow was a Mason and a trustee of the Rutgers Presbyterian Church and the Elberon, N. J., Memorial Church. His summer home was in Allenhurst, N. J.

His wife, Mrs. Grace White Bigelow, died in 1916. Surviving is a step-daughter, Mrs. Walter Simpson, of East Orange, N. J. (See also February JOURNAL, page 190 and March JOURNAL, page 270.)

SOCIETIES AND COLLEGES.

NEW YORK PHARMACEUTICAL COUNCIL.

The New York Pharmaceutical Council held a Victory Fair Trade Convention Exhibit and Banquet, April 13th–14th. The member Associations are:

Bronx County Pharmaceutical Association, Consolidated Brooklyn Retail Pharmacists, Inc., Italian Pharmaceutical Association, Long Island City Pharmaceutical Association, New York Academy of Pharmacy, New York Branch of AMERICAN PHARMACEUTICAL ASSOCIATION, New York County Pharmaceutical Association, New York German Apothecaries' Society, North Brooklyn Pharmaceutical Association, North Queens Pharmaceutical Association, North Shore Pharmaceutical Association, Queens County Pharmaceutical Association, Retail Druggists' Association of New York, Inc., Staten Island Pharmaceutical Association.

The General Committee is composed of: *Chairman*, Sol Fierer; *Secretary*, Milton S. Malakoff; *Treasurer*, F. C. A. Schaefer; and *Ex-Officio*, F. L. Grennie.

The Advisory Committee is composed of: W. C. Anderson, H. V. Arny, Morris Brodkin, J. L. Dandreau, J. H. Kidder, J. Leon Lascoff, Robert S. Lehman, H. H. Schaefer, C. P. Wimmer.

The convention was largely attended and President George D. Beal was one of the speakers; Secretary Kelly also attended the meeting. The annual address was delivered by President Frank L. Grennie and reports were rendered by the respective officers. Addresses were made by chairmen of Committees, followed by discussions. The following and others participated. George W. Mather, Morris Brodkin, John F. O'Brien, George M. Gales, George Gottesman, Miss Frances Kneitel, Roy Sterne and Mark Eisner.

STATE ASSOCIATIONS.

Meetings of the Fifth District of the N. A. B. P. comprising the states of Iowa, Nebraska, North Dakota, South Dakota and Minnesota, were held during the convention of the Minnesota State Pharmaceutical Association. The meeting was held Monday, April 5th, Hotel St. Paul.

Problems relating to Board of Pharmacy work were discussed by members of the different State Boards of Pharmacy, Dean Charles H. Rogers of the College of Pharmacy, University of Minnesota, discussed the relationship of Colleges of Pharmacy and State Boards of Pharmacy.

Plans are going forward for the annual convention of the Nebraska Pharmaceutical Association to be held May 3rd to 6th at the Cornhusker Hotel, Lincoln.

The dates for the Fifty-eighth Annual Convention of the North Carolina Pharmaceutical Association have been announced—they are Monday, Tuesday and Wednesday, May 10th, 11th and 12th. The convention will be held in Raleigh, and the Sir Walter Hotel will be convention headquarters.

The general assembly of South Carolina has ratified a bill to add barbiturates to the list of drugs the sale of which is regulated by the state's anti-narcotic law.

VIRGINIA PHARMACEUTICAL SYMPOSIUM.

The Second Annual Pharmaceutical Symposium will be held at the Medical College of Virginia on May 20th–21st. The program for the first day includes addresses by President Sanger of the College, and Dean Rudd of the pharmacy department.

Speakers on the first day include: Dr. R. A. Deno, on "The Pharmacy of Gland Products;" Dr. J. C. Forbes, on "The Extraction and Use of Stomach and Liver Preparation;" and Dr. R. J. Main, on "Therapeutics of Sex Hormones."

Discussions on the second day will be led by Dr. F. P. Fletcher, on the "Application of First Aid Treatment" by the pharmacist; G. E. Snider and T. D. Rowe on the "Antiseptic Value of Some Commonly Used Pharmaceutical Preparations;" and Dr. W. G. Crockett on "Bridging the Gap Between the U. S. P. X and U. S. P. XI."

PHI DELTA CHI.

The Grand Council of the Phi Delta Chi Fraternity, national professional fraternity of Pharmacy and Chemistry, was held in Indianapolis, Indiana, February 11th, 12th, 13th. Delegates from 17 chapters attended.

An outstanding feature of the convention was a visit to the plant and laboratories of Eli Lilly and Company.

Howard L. Reed, of the Massachusetts College of Pharmacy, Boston, was elected *Grand President* of the Council, succeeding J. Earle Galloway, of the Des Moines College of

Pharmacy. Arthur K. Lear, San Francisco, was elected *Grand Vice-President*. Officers, reëlected, were C. V. Nichols, Anadarko, Oklahoma, *Grand Treasurer*, and Rand P. Hollenback, Columbus, Ohio, *Grand Secretary* and *Editor*.

PURDUE CONFERENCE.

One entire session of the business conference conducted at Purdue University was devoted to the professional side of drug store operation. More than four hundred druggists attended this Seventh Annual Conference. Henry W. Heine was in charge of extension activities.

KANSAS BOARD.

Otto H. Keuther, of Herington, and W. F. Sprague, of Fredonia, have been appointed to the Kansas State Board of Pharmacy by Governor Walter A. Huxman, to fill the places of Joseph Paradowsky, *President*, and Pat Mulligan, *Secretary*, whose terms expire. The new appointments will become effective June 1st.

WYOMING BOARD.

Appointments to the Wyoming State Pharmacy Commission made by Governor Leslie A. Miller and ratified by the state senate are Ray Dame, Casper, to serve from June 10, 1936, to March 1, 1941 (filling the unexpired term of Tarvin Hoops of Cody), and R. C. Shultz, Worland, for a six-year term starting March 31, 1937.

DISTRICT THREE MEETING.

The annual meeting of District 3 of the National Association Boards of Pharmacy, and of the National Association Colleges of Pharmacy, was held at Charleston, S. C., April 21st and 22nd. Among those present at the meeting were President George A. Moulton of the National Association of Boards of Pharmacy, and Secretary H. C. Christensen.

A theme of discussion related to the requirements for pharmacy certificates in the different states.

COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN.

The Sixth Annual Pharmaceutical Conference of the College of Pharmacy of the University of Michigan will be held on Tuesday, May 18th, under the chairmanship of Prof. Howard B. Lewis, Director of the College of Pharmacy. The 1937 Conference will center its program around the contribution of pharmacy to public health and the coöperation of the pharmaceutical profession with the other public health agencies. An unusually interesting program has been prepared. A special invitation to all interested in the advancement of pharmacy is extended for the Conference.

The session will begin at 2:30 with a brief address of welcome by Dean Edward H. Kraus of the College of Literature, Science and the Arts of the University of Michigan. Dean Edward Spease of Western Reserve University will be guest speaker. He has done pioneer pharmaceutical work in hospitals, and will speak on "The Contribution of the Pharmacist to the Public Health." The second speaker will be Dr. Erwin E. Nelson, Professor of Pharmacology at the University of Michigan.

TITLE OF PHARMACIST.

A Bill has been introduced into the House of Lords (Great Britain) for the purpose of substituting the words "registered pharmacists or authorised sellers of poisons within the meaning of the Pharmacy and Poisons Act, 1933," for the words "entitled under the Pharmacy and Poisons Acts, 1852 to 1933, to use the title chemist and druggist" in Section 41 (2) of the National Health Insurance Act, 1936.—*The Chemist and Druggist.*

BARBITURATES SALES LIMITED IN ONTARIO.

Retail sales of barbituric acid and amidopyrine and their derivatives and of codeine and its salts (with certain exceptions) have been restricted to the filling of prescriptions of legally qualified physicians, dentists and veterinarians by a new law (No. 108—1937) enacted by the Ontario legislature. In addition, the Lieutenant-Governor in Council is authorized to amend the list of drugs affected, by addition or deletion on thirty days' public notice.

Prescribers and dispensers may be required to report the quantity of the specified drugs which they have prescribed or sold, and disciplinary action is provided for in cases of excessive or improper prescribing or sale.

The law defines the substances, to which the limitation of sales applies as follows:

Codeine and its salts in any form, except when combined with other medicinal ingredients, and not exceeding one-half of one grain of codeine or its salts and not less than the amount set by the British Pharmacopœia as a minimum dose of one of the other medicinal

ingredients, in each maximum dose of the combination, but where the combination contains two or more such ingredients having a similar action, the minimum dose of each ingredient, may be reduced to one-half the pharmacopœial dose where two ingredients are used, and to one-third where three ingredients are used, and where the combination contains less than one-half of one grain of codeine or its salts in a maximum dose of the combination the minimum dose of such ingredients may be reduced in proportion to the reduction in codeine.

Amidopyrine and barbituric acid (malonylurea) and derivatives or combinations of either of them with other substances whether sold separately or combined with other substances and whether sold under their proper name or under any trade name, mark or designation.—From *Oil, Paint and Drug Reporter*, April 12, 1937.

TEXAS LEGISLATION.

House Bill 1024, recently introduced in the Texas Legislature by Representative Heflin, would require that labels on medicine, drugs, cosmetics, biologicals, anti-toxins, serums and ampuls show date of manufacture, and prohibit the sale of the products which are more than two years old.

BOOK NOTICES AND REVIEWS.

Quantitative Pharmaceutical Chemistry. By GLENN L. JENKINS, Ph.D., Professor of Pharmaceutical Chemistry, College of Pharmacy, University of Minnesota, and ANDREW G. DUMEZ, Ph.D., Professor of Pharmacy and Dean of the School of Pharmacy, University of Maryland. Second edition, 466 pages, 5½ x 8, illustrated. Price, $3.50. McGraw-Hill Book Co., New York, 1937.

To those acquainted with the previous edition it is only necessary to state that the new one is a decided improvement. The added matter on calculations was undoubtedly needed and might have been enlarged even more. The increased size in other directions was in part necessitated by revisions of the Pharmacopœia and Formulary, but the additional references, problems and exercises and enlargement of the chapter on hydrogen-ion concentration add much to value of the book. The deletion of description and exercises on ultimate analysis may be regretted by some and, while agreeing with the statement that "a comprehensive treatment of this subject belongs in a course in organic analysis," some might yet insist that a knowledge of the fundamentals is desirable, even if no exercises are performed.

As a whole the book is excellent in most respects and the revised volume should be available to every student in every school of pharmacy in the country.—E. V. LYNN.

A Text-Book of Pharmacology and Therapeutics of the Action of Drugs in Health and Disease. By ARTHUR R. CUSHNY, M.A., M.D., LL.D. Eleventh edition, revised by C. W. Edmunds, A.B., M.D., Professor of Materia Medica and Therapeutics and Director of the Pharmacological Laboratories in the University of Michigan, Ann Arbor, and J. A. Gunn, M.A., M.D., D.Sc., Professor of Pharmacology and Director of the Nuffield Institute for Medical Research, University of Oxford, Oxford, England. Cloth. Price, $6.50. Pp. 808, with 70 illustrations. Published by Lea & Febiger, Philadelphia, Pa.

A Manual of Therapeutics. Modern Treatment and Formulary. By EDWARD A. MULLEN, P.D., M.D., F.A.C.S., Assistant Professor of Pharmacology and Physiology, Philadelphia College of Pharmacy and Science. Foreword by Horatio C. Wood, Jr., Professor of Therapeutics in University of Pennsylvania Graduate School of Medicine. Cloth: 4½ x 8 inches; pages 707. Price, $5.00. Published by F. A. Davis Company, Philadelphia, Pa.

The Cosmetic Formulary. How to Make Cosmetics, Perfumes, Soaps and Allied Products. By Editor-in-Chief, H. BENNETT, F.A.I.C. Cloth: 6 x 9 inches; pages xix + 279. Price, $3.75. Published by Chemical Publishing Co. of New York, Inc.

Williams' Anatomy and Physiology, New (5th) Edition—thoroughly revised. By JESSE FEIRING WILLIAMS, M.D., Professor of Physical Education, Teachers College, Columbia University. 606 pages, 416 illustrations. Cloth, $2.75 net. The essentials of body structure and function are brought out impressively by Dr. Williams. This text leads the student through anatomy and physiology in an orderly advance, step-by-step. W. B. Saunders Company, Philadelphia, Pa.

List of Trade Names, by AMERICAN DRUG MANUFACTURERS' ASSOCIATION, Washington, D. C. Price, 50 cents.

American Medical Dictionary, by W. A. NEWMAN DORLAND. Publishers, W. B. Saunders Company, Philadelphia, Pa. Price, $7.00.

The Structure and Composition of Foods, by ANDREW L. and KATE WINTON. Publishers, John Wiley & Sons, Inc., New York City. Price, $15.00.

Toxicology, Underhill, by THEODORE KOPPANYI. Publishers, P. Blakiston's Son & Company, Philadelphia, Pa. Price, $2.50.

(*To be continued.*)

NOTICE TO CONTRIBUTORS TO THE JOURNAL AMERICAN PHARMACEUTICAL ASSOCIATION.

The following notice has been prepared from comments received from members of the Board of Review of Papers and of the Publication Committee.

Manuscripts should be sent to Editor E. G. Eberle, 2215 Constitution Ave., N. W., Washington, D. C.

All manuscripts should be typewritten in double spacing on one side of paper 8½ x 11 inches, and should be mailed in a flat package—not rolled. The original (*not* carbon) copy should be sent. The original drawings, not photographs of drawings, should accompany the manuscript. Authors should indicate on the manuscript the approximate position of text figures. All drawings should be marked with the author's name and address.

A condensed title running page headline, not to exceed thirty-five letters, should be given on a separate sheet and placed at the beginning of each article.

The method of stating the laboratory in which the work is done should be uniform and placed as a footnote at end of first page, giving Department, School or College. The date when received for publication should be given.

Numerals are used for figures for all definite weights, measurements, percentages, and degrees of temperature (for example: 2 Kg., 1 inch, 20.5 cc., 300° C.). Spell out all indefinite and approximate periods of time and other numerals which are used in a general manner (for example: one hundred years ago, about two and one-half hours, seven times).

Standard abbreviations should be used whenever weights and measures are given in the metric system, *e. g.*, 10 Kg., 2.25 cc., etc. The forms to be used are: cc., Kg., mg., mm., L. and M.

Figures should be numbered from 1 up, beginning with the text-figures (line engravings are always treated as text-figures and should be designed as such) and continuing through the plates. The reduction desired should be clearly indicated on the margin of the drawing. All drawings should be made with India ink, preferably on white tracing paper or cloth. If coördinate paper is used, a blue-lined paper must be chosen. Usually it is desirable to ink in the large squares so that the curves can be more easily read. Lettering should be plain and large enough to reproduce well when the drawing is reduced to the width of a printed page (usually about 4 inches). Photographs intended for half-tone reproduction should be securely mounted with colorless paste.

"Figure" should be spelled out at the beginning of a sentence; elsewhere it is abbreviated to "Fig.;" per cent—2 words.

The expense for a limited number of figures and plates will be borne by the JOURNAL; expense for cuts in excess of this number must be defrayed by the author.

References to the literature cited should be grouped at the end of the manuscript under the *References*. The citations should be numbered consecutively in the order of their appearance (their location in the text should be indicated by full-sized figures included in parentheses). The sequence followed in the citations should be: Author's name (with initials), name of publication, volume number, page number and the date in parentheses. Abbreviations for journals should conform to the style of *Chemical Abstracts*, published by the American Chemical Society.

(1) Author, A. Y., *Am. J. Physiol.*, 79, 289 (1927).

Papers presented at the Sections of the AMERICAN PHARMACEUTICAL ASSOCIATION's annual meeting become the property of the Association and may at the discretion of the Editor be published in the JOURNAL. Papers presented at these Sections may be published in other periodicals only after the release of the papers by the Board of Review of Papers of the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION.

The Editor will appreciate comments from Board of Review and Committee on Publication, members, authors and others interested.

GEORGE C. CLOSE.

GEORGE C. CLOSE, member of the first graduating class (1831) of the College of Pharmacy of the City of New York, whose diploma is shown here, was born at Stamford, Conn., February 9, 1812, the son of Thomas Close, M.D. He died January 15, 1891.

He had served his *Alma Mater* as trustee, vice-president and president. Mr. Close became a member of the AMERICAN PHARMACEUTICAL ASSOCIATION in 1858, at the meeting held in Washington, D. C., and in 1865–1866 was one of its vice-presidents.

He was a frequent contributor to the proceedings of the ASSOCIATION; a paragraph from an article on "Practical Notes and Observations" (1871), which characterized him is quoted:

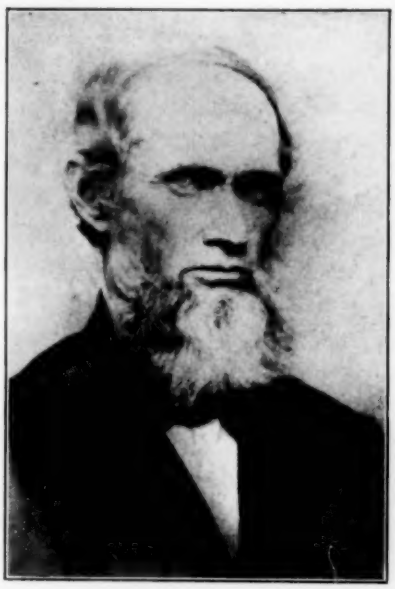
"Believing it to be the duty of every member of this ASSOCIATION to communicate to his brethren the results of any observations he may have made, which are conducive to their interests or public health, I have concluded, at the risk of being thought presumptuous, to throw in my mite." When the Alumni Association of the New York College of Pharmacy collected funds for their new building, Mr. Close subscribed with these words: "My class subscribes $10.00 for each man, and as I am the only one left, I will pay for the others as well as for myself."

He was one of the founders of Kings County Pharmaceutical Association and its first president; a member of the Long Island Historical Society and took a great interest in its work.

The first diploma, issued to George C. Close, in 1831.

Names on the Diploma besides that of the recipient: Dr. Smith Rogers, Dr. John Torrey, Oliver Hull, H. H. Schieffelin, *President;* Lindley Murray, John L. Embree, Constantine Adamson.

Mr. Close's pharmacy, in 1865, was located at 106 Fulton Street, Brooklyn; in 1870, he removed to the corner of Smith and Schermerhorn Streets, where he remained until about 1884, when he retired from active business. He was of an alert, active mind and clear intellect, he was interested in all scientific progress to the day of his death.



GEORGE C. CLOSE.

L. K. DARBAKER.